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THE WESTERN Journal of Medicine

VOLUME 125 • NUMBER 1 JULY 1976

SPECIAL BICENTENNIAL ISSUE ▪ SEVEN VIEWS OF MEDICINE AND THE QUALITY OF LIFE ▪ A SECTION ON MEDICINE AND AMERICAN HISTORY ▪ A NEW SERIES ON INFECTIOUS DISEASE EMERGENCIES ▪ MEDICAL PROGRESS: MYCOPLASMA PNEUMONIAE INFECTIONS ▪ OTHER CONTENTS ON THIRD PAGE

The ultimate objective test: sleep laboratory proof of effectiveness ... now in geriatric insomnia patients

Six female insomniacs, ranging in age from 67 to 82 years received Dalmane (flurazepam HCl) for seven consecutive nights in the sleep research laboratory.[1] Improvement over pre-treatment baseline levels was significant for sleep induction and sleep maintenance ($p < .05$). And the greater the sleep problem in these patients, the better the effect with Dalmane (significant correlation at $p < .01$ level).

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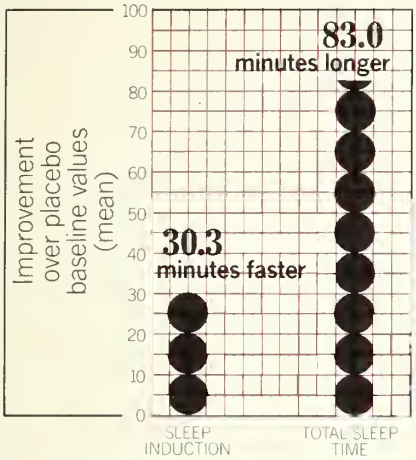
Elderly insomniacs fell asleep faster, slept longer[1]



Results expand and confirm objective proof of efficacy in younger adults with insomnia

The effectiveness of Dalmane (flurazepam HCl) was demonstrated in earlier studies of 32 younger adults with trouble falling asleep, staying asleep or sleeping long enough.[2] On average, in these studies, Dalmane induced sleep within 17 minutes and provided 7 to 8 hours of sleep, at the same time reducing number of nighttime awakenings.

Relative safety, even in patients on warfarin

Morning "hang-over" has been relatively infrequent with Dalmane. And no unacceptable fluctuation in prothrombin time has been reported in warfarin patients on Dalmane.[2,3] The usual adult dosage is 30 mg *h.s.*; in elderly and debilitated patients, limit initial dosage to 15 mg to help preclude oversedation, dizziness or ataxia.

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES:

1. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
3. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641

New evidence proves insomnia relief in elderly patients

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THE WESTERN Journal of Medicine

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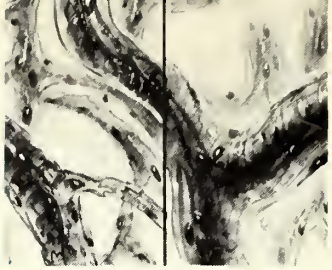
When women outlive their ovaries...



The menopausal "flush" is believed to result from an autonomic nervous system imbalance due to estrogen deficiency. Here, illustration shows artist's interpretation of "normal" vs. dilated arteriole-capillary-venule network.

"It seemed like I was having one flush after another. It wasn't just a nuisance... it was a real problem."

The menopausal flush is the classic sign of estrogen deficiency...generally recognized as a clear indication for treatment.

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This wasn't always the case.

There was a time when the symptoms of the menopause went untreated...when women were expected to suffer the severe flushes and sweats of estrogen deficiency in silence or, at best, with a minimum of encouragement and understanding.

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Three studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. For further information see "Warnings" in prescribing information.

For the classic symptoms of the menopause

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See next page for revised prescribing information.

BRIEF SUMMARY
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Actions: Estrogens are responsible for development and maintenance of the female reproductive system and secondary sex characteristics. They cause the growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Estrogens are also involved in psychologic and emotional aspects of feminine behavior. As estrogen levels increase during the menstrual cycle, there is a sense of vigor and well-being, and in the menopausal period estrogens aid in relieving nervous symptoms (e.g. anxiety, depression and irritability) due to estrogen deficiency. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the pre- or non-ovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens do not induce ovulation.

Estrogens affect calcium and phosphorus metabolism, and are involved in maintenance of normal bone structure. In prolonged estrogen deficiency states, administration of estrogen acts to prevent associated bone degenerative changes.

Estrogens appear to be responsible for the relatively greater amount of alpha-lipoprotein and correspondingly lower amount of beta-lipoprotein found in premenopausal women as compared with men.

Estrogens affect the release of pituitary gonadotropins and may also deplete the gonadotropic content of the pituitary.

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause, senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.

Warnings: Three separate studies have reported an increased risk of endometrial carcinoma in association with the postmenopausal administration of exogenous estrogens. Smith *et al.*[1] retrospectively compared the records of 317 patients with endometrial carcinoma with the records of an equal number of contrast patients having cervical, ovarian, or vulvar neoplasms. The unadjusted relative risk estimate of endometrial cancer was 4.5 times greater in women exposed to estrogen therapy. The type of estrogen used, the preparation, and the dosage were not considered in this study. These factors may play a role in modifying the average relative risk found in this study. The authors also suggested that there may be a relationship between increasing risk and the duration of administration, however, the data are not conclusive on this point. A second retrospective study reported by Ziel and Finkle[2] examined the records of 94 patients with endometrial carcinoma and those of a two-fold contrast series from the same health plan population. The estimate of relative risk was found to be 7.6. In addition, the authors reported a relative risk estimate of 5.6 for a duration of exposure of 1 to 4.9 years, and 13.9 for exposure of 7 or more years. In this study, conjugated estrogens were reported to be the type of estrogen used. Mack *et al.*[3] retrospectively studied 63 cases of endometrial carcinoma and a four-fold contrast group. The relative risk of endometrial carcinoma was estimated to be 8.0 for any estrogen usage, and 5.6 for conjugated estrogen usage. The relationship between relative risk and duration of use could not be conclusively described from the data in the study.

Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.

Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations. Such physical examinations should be repeated at regular intervals, at least annually, during estrogen therapy.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Estrogen usage may cause preexisting fibromyomata to increase in size, therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.

Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
increased incidence of gallbladder disease
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest

Dosage and Administration: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) should be administered cyclically (3 weeks of daily estrogen and 1 week off). There should be an annual reassessment of the patient to determine the need for continued estrogen therapy. This assessment may be assisted by lowering the dose and observing the symptoms to determine correct maintenance dosage for continued therapy.

Menopausal Syndrome—1.25 mg daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (e.g. osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg to 1.25 mg daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically.

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(POSTERIOR VIEW OF PANCREAS)

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the compatible vasodilator

*Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500, 1000, 5000 and Unit Dose.

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Testing in Humans: Who, Where & When.

the weight of ethical opinion:

Few would disagree that the effectiveness and safety of any therapeutic agent or device must be determined through clinical research.

But now the *practice* of clinical research is under appraisal by Congress, the press and the general public. Who shall administer it? On whom are the products to be tested? Under what circumstances? And how shall results be evaluated and utilized?

The Pharmaceutical Manufacturers Association represents firms that are significantly engaged in the discovery and development of new medicines, medical devices and diagnostic products. Clinical research is essential to their efforts. Consequently, PMA formulated positions which it submitted on July 11, 1975, to the Subcommittee on Health of the Senate Labor and Public Welfare Committee, as its official policy recommendations. Here are the essentials of PMA's current thinking in this vital area.

1. PMA supports the mandate and mission of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and offers to establish a special committee composed of experts of appropriate disciplines familiar with the industry's research methodology to volunteer its service to the Commission.

2. PMA supports the formation of an independent, expert, broadly based and representative panel to assess the current state of drug innovation and the impact upon it of existing laws, regulations and procedures.

3. When FDA proposes regulations, it should prepare and publish in the *Federal Register* a detailed statement assessing the impact of those regulations on drug and device innovation.

4. PMA proposes that an appropriately qualified medical organization be encouraged to undertake a comprehensive study of the optimum roles and responsibilities of the sponsor and physician when company-sponsored clinical research is performed by independent clinical investigators.

5. PMA recognizes that the physician-investigator has, and should have, the ultimate responsibility for deciding the substance and form of the informed consent to be obtained. However, PMA recommends that the sponsor of the experiment aid the investigator in discharging this important responsibility by providing (1) a document detailing the investigator's responsibilities under FDA regulations with regard to patient consent, and (2) a written description of the relevant facts about the investigational item to be studied, in comprehensible lay language.

6. In the case of children, the sponsor must require that informed consent be obtained from a legally appropriate representative of the participant. Voluntary consent of an older child, who may be capable of understanding, in addition to that of a parent, guardian or other legally responsible person, is advisable. Safety of the drug or device shall have been assessed in adult populations prior to use in children.

7. PMA endorses the general principle that, in the case of the mentally infirm, consent should be sought from both an understanding subject and from a parent or guardian, or in their absence, another legally responsible person.

8. Pharmaceutical manufacturers sponsoring investigations in prisons must take all reasonable care to assure that the facilities and personnel used in the conduct of the investigations are suitable for the protection of participants, and for the avoidance of coercion, with a respect for basic humanitarian principles.

9. Sponsors intending to conduct non-therapeutic clinical trials through the participation of employee volunteers should expand the membership and scope of its existing Medical Research Committee, or establish such an internal Medical Research Committee, with responsibility to approve the consent forms of all volunteers, designs, protocols and the scope of the trial. The Committee should also bear responsibility to ensure full compliance with all procedures intended to protect employee volunteers' rights.

10. Where the sponsor obtains medical information or data on individuals, it shall be accorded the same confidential status as provided in codes of ethics governing health care professionals.

11. PMA and its member firms accept responsibility to aid and encourage appropriate follow-up of human subjects who have received investigational products that cause latent toxicity in animals or, during their use in clinical investigation, are found to cause unexpected and serious adverse effects.

12. PMA supports the exploration and development by its member companies of more systematic surveillance procedures for newly marketed products.

13. When a pharmaceutical manufacturer concludes, on the basis of early clinical trials of a basic new agent, that a new drug application is likely to be submitted, a proposed development plan accompanied by a summary of existing data, would be submitted to the FDA. Following a review of this submission, the FDA, and its Advisory Committee where appropriate, would meet with the sponsor to discuss the development plan. No *formal* FDA approval should be required at this stage. Rather, the emphasis should be on identification of potential problems and questions for the sponsor's further study and resolution as the program develops.

The PMA believes that health professionals as well as the public at large should be made aware of these 13 points in its Policy on Clinical Research. For these recommendations envisage constructive, cooperative action by industry, research institutions, the health professions and government to encourage creative and workable responses to issues involved in the clinical investigation of new products.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D. C. 20005

However you define in acute cystitis achieved an

*In a new study 8 out of 10 patients with acute lower urinary tract infection, primarily cystitis, achieved sterile urine. All infections were nonobstructed. Susceptible organisms included *E. coli*, *Klebsiella-Aerobacter*, *Proteus mirabilis* and *Proteus vulgaris*.

No. of patients	Sterile urine	Clear culture <1000 organisms/ ml urine	Clear culture <10,000 organisms/ ml urine
406	81% (330)	83% (339)	88% (357)

Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey

clear culture

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(sulfamethoxazole)

81% to 88% cure rate*

Gantanol® B.I.D.
sulfamethoxazole/Roche

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

Basic therapy with convenience and economy in acute nonobstructed cystitis†

†due to susceptible organisms

ROCHE

Please see following page for summary of product information.

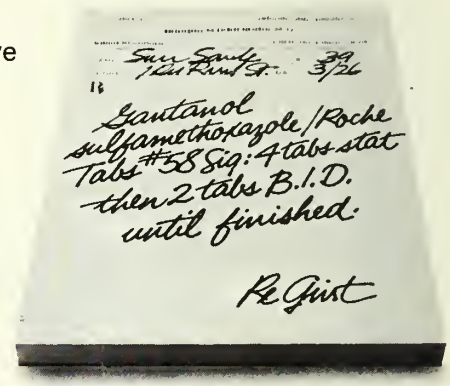
Gantanol® B.I.D.

sulfamethoxazole/Roche

Basic therapy with convenience and economy in acute nonobstructed cystitis*

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

- Effective in nonobstructed cystitis.
- Active against susceptible strains of gram-negative and gram-positive organisms: *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*
- Rapid antibacterial blood and urine levels—in from 2 to 3 hours.
- Convenient, economical B.I.D. dosage.
- Contraindicated during pregnancy and the nursing period and in infants under 2 months of age.
- As with all sulfonamides, adequate fluid intake should be maintained during therapy; perform frequent CBC's and urinalyses with careful microscopic examination.



*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily nonobstructed pyelonephritis, pyelitis and cystitis) due to susceptible organisms, usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.* **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

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Division of Hoffmann-La Roche Inc.
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IN GONORRHEA

INJECTION

Wycillin®

(STERILE PENICILLIN G PROCAINE SUSPENSION) WYETH

In **Gonorrhea,** the drug regimen of choice is aqueous penicillin G procaine. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given just before injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular penicillin G procaine—*N. gonorrhoeae:* acute and chronic (without bacteremia).

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large single dose is administered in the treatment of gonorrhea (4.8 million units). These reactions may be manifested by mental disturbances, including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death". The reactions noted in carefully controlled studies occurred in approximately one in 500 patients treated for gonorrhea. Reactions are transient, lasting from 15-30 minutes.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 ml. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations have been reported (see "Warnings"). Procaine hypersensitivity reactions have not been reported with this drug.

Dosage and Administration: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, given just before injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units aqueous penicillin G procaine daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each disposable syringe 2,400,000 units (4-ml. size) contains penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.5% lecithin, 0.5% carboxymethylcellulose, 0.5% povidone, 0.1% methylparaben, and 0.01% propylparaben. The multiple-dose 10-ml. vial contains per ml. 300,000 units penicillin G procaine in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. povidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® L-A
(STERILE PENICILLIN G BENZATHINE SUSPENSION) WYETH

Syphilis is preferably treated with penicillin G benzathine, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine. —Venereal infections: Syphilis, yaws, bejel and pinta.

For deep intramuscular injection only.

Contraindication: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Dosage and Administration: Venereal infections —

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: Units penicillin G benzathine (as active ingredient): 2,400,000 units in 4-ml. single dose disposable syringe. Each disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. 300,000 units per ml.—10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben, and 0.14 mg. propylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

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Medicine and the Quality of Life

In the world of medicine and health care there is growing talk of something called quality of life. In contemporary society there is beginning to be talk of making this something available to every person. Quality of life for anyone is always a stimulating idea, and quality of life for everyone evokes a disquieting yet stirring dream of a new goal that just could be a destined future for this great nation.

But what is meant by quality of life? It is by no means defined. For many, like Alice in Wonderland it seems to mean "what I want it to mean." There is need for some description, even measurement. Obviously it involves such things as one's heredity, cultural heritage and experience, physical and emotional maturation, and something called personal fulfillment. Today's technologic, social, economic and even political interdependence among people everywhere is part and parcel of anyone's and everyone's quality of life. And, to be sure, the quality of the environment must be adequate for the needs of each individual person and for the long-term survival and development of humankind on this earth. And much else is involved.

Quality of life is increasingly cited as a goal for medicine and health care. Obviously, it is something physicians should and do seek for their patients. But perhaps more is being asked of medicine. What other profession can be any closer to this concept, which is so intimately linked to individual and personal physical, mental, emotional and, yes, social well-being? There are evident expectations that medicine will somehow bring about a better quality of life. But it is not clear just what is meant by quality of life, or just how or to what extent medicine and health care can bring about its improvement. Yet the idea of quality of life, and quality of life for all, seems to be gaining ground, and one cannot quite put aside the notion that this idea may be just as visionary and just as worthy of America today as was the vision of the founding fathers for the era that lay ahead of them 200 years ago.

The editors of The Western Journal of Medicine propose, as part of their contribution to America's bicentennial, to provide a forum for a dialogue and discussion of the relationship of medicine and quality of life. The forum is initiated with the statements beginning on the following page. Readers and others are invited to submit their views equally constructively and succinctly. As many of these as space permits will be published in future issues of the Journal. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement on "Medicine and the Quality of Life" to summarize the dialogue and discussion that has taken place.

The seven statements that follow are the views of persons who are distinguished (or in the case of a medical student—certain to be distinguished) contributors to thought on this subject. It is the hope of the editors that their views on this timely and important subject will provoke additional views and comment from among our readers.

—MSMW

Refer to: Watts MSM (Ed): Medicine and the quality of life—A forum. West J Med 125:1, Jul 1976

A New Perception of Medicine's Role

THEODORE COOPER, MD, PhD, Washington, D.C.
Assistant Secretary for Health, United States Department of Health, Education, and Welfare

BECAUSE OF THE immense contribution medicine has made to the advancement of human welfare in the last 100 years, there is an understandable inclination to anticipate, indeed to expect, more of the same in the decades ahead. Not only do we take it for granted that the less developed nations of the world will appropriate the principles and techniques of modern medical care for the benefit of their own populations, we also assume that the engine of biomedical research will continue to produce new knowledge that will render the chronic and degenerative diseases as susceptible to medical management as are the communicable diseases. Thus, I think that health professionals and laymen alike accept almost as an article of faith that medicine is and will continue to be a primary avenue toward improvement in the quality of life for all mankind.

I would not suggest that such faith is misguided, but I think we in medicine and the public generally are at the risk of taking for granted a role in improving the quality of life that medicine may not be able to play.

While I personally find it rather difficult to define "the quality of life" in terms that seem appropriate and meaningful for the vast spectrum of conditions in which human beings live and for the broad range of ideologies, political and otherwise, to which they subscribe, it does seem credible that all people want to enjoy good health and want access to those things, including medical care, that preserve or restore health. But that does not mean that we in the medical profession can expect to advance the quality of life for future generations merely by refining and enlarging the precepts and methods that have made the past century the most productive and successful period in the history of medicine. For it is becoming more and more obvious that further advances in health will likely result less from the provision of medical services than from improved socioeconomic status and changes in man's environment and behavior, none of which is substantially amenable to medical intervention.

If up to 80 percent of all cancer results from exposure to carcinogenic agents in the environment, what part does medicine play in solving this health problem? Similarly, if cardiovascular disease and stroke are increasingly found to be associated with life-style, what can medicine expect to accomplish? Much the same question can be posed with respect to accidental injury and death and the vast if uncounted amount of emotional and physical illness that common sense and experience tell us is associated with what has been called "the stress of modern living." Beyond any doubt, all of these diminish the quality of life for the individual person and for society because they compromise health. Yet I think we must concede that contemporary medicine is ill-equipped to address these problems with the same vigor and confidence of success that has marked the last century.

"If up to 80 percent of all cancer results from exposure to carcinogenic agents in the environment, what part does medicine play in solving this health problem?"

Does this imply, then, that medicine will have a reduced role in the future effort to improve the quality of life? Have we, in fact, passed through the golden age of medical progress only to settle into a period of limited horizons and declining contribution to the welfare of mankind and the quality of human life? I certainly do not think so.

Refer to: Cooper T: A new perception of medicine's role, *In* Medicine and the quality of life—A forum. West J Med 125:2-3, Jul 1976

I do think, however, that the future contribution of medicine will have to be distinctly different from that of the past.

For one thing, medicine will have to give more than lip service to its responsibilities in the broadening field of prevention. In order to contribute to improving the quality of life, medicine will have to shift from its traditionally passive role—providing care when the patient asks for it, an essentially remedial role—to one of active involvement in seeking to address conditions in society that give rise to the very health problems that medicine is expected to solve. I am not suggesting that every physician become some kind of social activist or instant expert on problems of the economy, community planning, education, or any of the other societal factors that influence health and the quality of life. Not all of us are cut out for such things, and certainly no practicing physician can place some other concern ahead of the needs of his or her patients. But it does not make sense for the medical profession as a collective force to remain aloof from the very etiologic factors that cause a great many patients to seek help. Where once medicine had to concern itself with microbes, now it must focus on a new class of societal pathogens, one perhaps no less strange and baffling, and certainly no less important, than the invisible organisms that our predecessors learned to identify and to cope with.

There will always be room, I hope, for further advances in diagnosis, treatment and rehabilitation. We will find better and better ways to treat cancer and heart disease, to ease mental illness and to arrest the degenerative diseases. And every time such measures are brought to bear, the

" . . . medicine will have to give more than lip service to its responsibilities in the broadening field of prevention."

quality of a life will be improved. But improving the quality of all our lives and of the lives of future generations will demand more of medical science and practice, more of medical training, and more of the profession itself than the gradual accretion of new weapons and new skills. It will require a new perception of the role of medicine in society, a perception toward which I believe we are beginning to move—and none too soon.

A More Effective, Efficient and Equitable System

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MEDICINE HAS MADE many important contributions to the quality of life in America. During the past half century mortality has declined significantly for infants, children and young adults. True, part of this decline is attributable to nonmedical factors such as a higher standard of living, but in my opinion most of it stems from great advances in medicine's ability to prevent or treat infectious diseases, to deal with trauma and to intervene surgically with greater safety and efficacy.

In addition to raising life expectancy, medicine has contributed to a fuller, more satisfactory life for millions by correcting or reducing a wide variety of disabilities involving the senses, reproductive function, physical movement and organ failure. Finally, medicine has continued to provide sympathy, reassurance and caring.

Most of these contributions are now taken for granted, and the dominant public mood is "What have you done for me lately?" The scientific advances have often been closely associated with increased specialization—which frequently has negative implications for access to, for continuity of and for personal quality of care. Moreover, many of the advances (and pseudoadvances) of the past 15 years have been very expensive, so that each additional reduction in mortality or morbidity now requires a massive diversion of resources from other purposes. Some technologic advances, which are viewed not so much as extending life as prolonging dying, may actually adversely affect the quality of life.

" . . . the dominant public mood is 'what have you done for me lately?' "

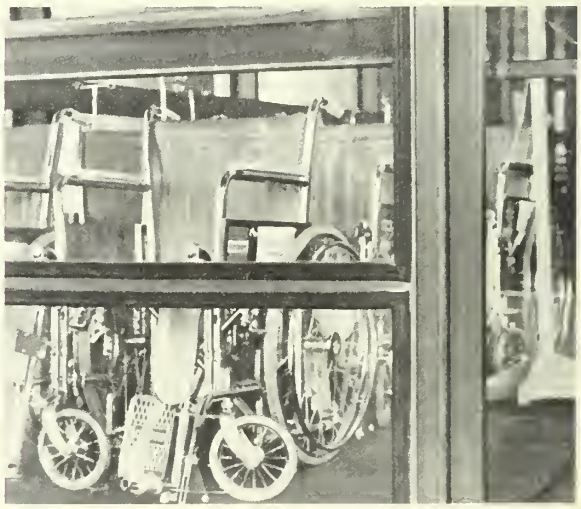
Another negative factor is the growth of iatrogenic disease. Powerful drugs and radical surgical procedures are two-edged swords in the battle to improve the quality of life. The increasing complexity of modern medical and surgical interventions is making it more and more difficult for physicians to heed the ancient injunction, "do no harm." Even "relief of anxiety," a staple item in every physician's output, often enters the quality-of-life equation with a negative sign because of the proliferation of diagnostic tests with numerous false positives.

What of the future? Significant breakthroughs in the treatment of arteriosclerosis, cancer and mental illness could contribute greatly to the quality of life—although much would depend on the nature of the treatment. Even as the search for such breakthroughs continues, it seems to me that medicine should consider the possibility of *contributing more* by *doing less*. Lest this sound paradoxical, recall that while physicians regard medical care as a good thing, most lay persons regard it as a necessary evil. The difference in point of view is fundamental. If physicians devoted as much time, energy and skill to minimizing the need for medical care as they now devote to its delivery, the quality of life might increase appreciably.

How can this be done? One step is the development and promotion of "self care," including care by family and friends. Self-care movements are burgeoning, both in this country and abroad. To be sure, some of them are simply fads, some are gimmicky and some may be dangerous frauds. At their best, however, they are attempts to give concrete expression to what every physician knows: an intelligent, informed lay person can deal with a large proportion of the acute and chronic conditions that are called illness. The trickiest part is making sure that those conditions requiring professional attention get it promptly.

Beyond encouraging and teaching self care, medicine could contribute to the quality of life by the promotion of health. This is surely not an easy task, since much that affects health is beyond the reach of medicine. Many physicians are moving in this direction, but more could be done. Medical schools in particular could increase the emphasis on the prevention of disease and the maintenance of health in their research and teach-

"If physicians devoted as much time, energy and skill to minimizing the need for medical care as they now devote to its delivery . . . . "



Refer to: Fuchs VR: A more effective, efficient and equitable system, *In* Medicine and the quality of life—A forum. West J Med 125:3-5, Jul 1976

ing. A physician emerging from a school with this emphasis would take a broad view of his or her duties and responsibilities. Instead of the yardstick of success being the length of the queue in the waiting room or the number of cases in which personal intervention dramatically altered the course of events, physicians would judge themselves collectively by improvements in the health levels of the populations they serve.

Of course, we should not ask too much of medicine, and medicine should not promise more than it can deliver. The quality of life depends on many things besides health, and health depends upon many things besides medical care. But given the high visibility of health problems, and given medical care's share of the gross national product (over 8 percent), significant improvement in our health system could have major spin-offs for other sectors. As the United States enters its third century, let us hope that the leaders of medicine will eschew taking bows for the contributions of the past, will abandon the myths that presently enthrall teaching and practice, and will start creating a more effective, efficient, and equitable system of health care. We can expect no more; we should ask no less.

Purposefulness in Human Life

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OUR UBIQUITOUS ADVERTISERS have done their best to bind the word "quality" to the idea of excellence. They urge us to buy quality meat, to rest at quality hotels and to enjoy quality entertainment. But any dictionary supplies a less alluring definition: quality means attribute, property, manner of feature. The quality of mercy is not its excellence, but its very nature. With this meaning in mind, we say, "well, he has his good and bad qualities." Aristotle lists quality as the third of the basic categories of being and defines it as "all the modifications of substance, such as heat and cold, whiteness and blackness, heaviness and lightness, in virtue of which bodies are said to alter."[1]

Modern medicine owes its origin and its success to the slow, but steady abandonment of qualitative notions of disease in favor of quantitive concepts. Richard Shryock writes, "Scholasticism had emphasized qualitative rather than quantitive tests, classification rather than measurement . . . seventeenth century scientists in revolting against scholasticism, reacted in particular against its qualitative lore."[2] The impetus which Galileo and Newton imparted to quantitative observation and theory and the invention of instruments for measurement stimulated schools of medical theory, iatrophysics and iastrochemistry, which are ancestral to modern medicine. Sanctorius, one of the earliest quantifiers and the inventor of a pulsometer and a thermometer, wrote, "in order to discover a true remedy, not only must the quality of the disease be known, but also its quantity, which measures the extent of departure from the normal."[3] Quantification makes possible the range of physiological standards that represent the normal and the measurement of individual deviation. Quantification produces the epidemiological statistics that establish the effectiveness of diagnostic and therapeutic procedures. Quantification permits the design of research leading to new drugs and techniques. Quantification is the basis of modern medicine. Sydenham recognized that fever indicated the presence of foreign matter in the body, but was limited to a qualitative description: "viscid humours" in the blood against which the animal spirits must struggle, exciting "the febrile ebullition." Today, counts of circulating granulocytes,

Refer to: Jonsen AR: Purposefulness in human life, *In* Medicine and the quality of life—A forum. West J Med 125: 5-7, Jul 1976

lymphocytes and eosinophils begin to warn of an invasion and even identify the invader before it is seen. No one would wish to return to the qualitative descriptions of historic medicine. Quantity, not quality, makes modern medicine possible and successful.

But, of course, we do speak of quality medicine. Some cynics would have it that this merely means that we do our quantitative work particularly well, that our research is statistically superb, our diagnostic tests are correctly calculated, our cure rates and morbidity and mortality tables accurately accumulated. However, it is often said today that quality medicine must be a medicine that contributes to the quality of life. Can this appealing but obscure idea serve as a criterion for the excellence of medicine? A hint of useful meaning might be found in the passage of Aristotle cited above.

After defining quality as the modifications of substance, Aristotle adds, "virtue and vice fall among these modifications, for good and evil indicate quality, especially among living things and particularly those living things which have purposes." The only living things "which have purposes" are, as far as we know, ourselves. We employ ratiocination to fit means to ends; we express intentions in symbolic communication: we make machines and establish institutions to attain certain goals. Whatever the adumbrations of these activities among our animal relatives, we alone do them pervasively and constantly. Aristotle's words suggest that the most basic meaning of quality of life refers to the ability of humans to formulate and implement purposes.

The variety of human purposes is infinite, their origin baffling and their execution erratic. Still, purposefulness is our most characteristic activity and, when it is stifled or frustrated, our humanness is blunted. Purposefulness is our glory: it is the wellspring of achievement, progress, invention and cooperation. But it is also the root of our griefs: persons can, and often do, form purposes that are discordant, conflicting and vicious. Out of purposefulness emerge both virtue and vice. The quality of purposefulness, then, is both our essence and our ambiguity as humans.

"Quantity, not quality, makes modern medicine possible and successful."

I would assert that the ultimate goal of medicine is to support the quality of purposefulness. This may seem remote from the immediate goals of medical activities—treating infections, managing blood pressure, resecting malignancies and so forth. However, all injury and illness, to a greater or less degree, affect purposefulness. They deflect persons from their set and spontaneous purposes and impose upon them the foreign purposes of fighting off their debility and rearranging their lives. Medicine, by reducing or eliminating the coercions of ill-health, serves human purposefulness. This is its first contribution to the quality of life.

This assertion is very simple to make and relatively simple to support. It is not so simple to apply. I perceive two major problems, the first of which is rather frequently discussed. The second, however, is less noticed and for that reason is possibly more harmful to quality medicine. The first problem arises from something intrinsic to many medical situations and activities. Because ill-health creates dependency, medical care can foster dependency rather than purposefulness. Because medical interventions are often quite specific and quite technical, those applying them can forget the more ultimate goal of restoring the patient to purposefulness. The set of problems that arise here are summed up in the slogans about the "patient as person," and treating the whole person. Modern medical care is frequently criticized for its failures in this respect.[4]

There is, however, a second and, in my opinion, a more insidious problem. Modern medicine has accomplished much in the understanding of acute and chronic disease. It is not surprising that a mythic power hangs like a halo around modern medicine. It is within the power of medicine, this myth intimates, to create good health. It is not the vagueness of this phrase, good health, which perturbs me, nor the vacuousness of the claim. Most sensible practitioners and their patients should be well aware of both vagueness and vacuousness. It is rather the implications of the myth that are troublesome.

Good health, to the extent that the words have meaning, seems to arise from a variety of factors over which medicine has little control. It is related to style of life, to social condition, to economic status, to environmental factors.[5] This is well known. But it is often not noticed that many of these conditions depend upon "good purposes." The adoption of certain life styles or

their promotion is a purposeful activity. Social structure and economic conditions result from the pursuit of certain purposes. The safety of the environment demands intervention with purposeful goals. The crucial problem, then, is that of distinguishing between good and bad purposes. One can proclaim that a healthy life style, a sound economy, a just society and a salubrious environment are good and are good for health. But within that proclamation lies a tangle of human purposes which are, more often than not, at odds. The current disputes over regulation of product safety and efficacy, over energy and environment, over welfare and taxation reveal the diversity of human purposes. Shall the debates be solved by fiat? Whose fiat? Whose purposes should prevail? Shall people and populations be made healthy by legislating away a broad range of human purposes hitherto considered legitimate? Are health and freedom incompatible? If so, how can medicine have as its ultimate goal the promotion of the basis of freedom, purposefulness?

These I consider the most serious ethical problems that face modern medicine. It must, on the one hand, aim to restore and strengthen the human quality of purposefulness. Thus, it aims to make persons free insofar as their freedom is coerced by ill-health. On the other hand, the conditions for health are often compromised by the very purposefulness medicine promotes. Should medicine, then, become a moralism, deciding what purposes are good and which bad? Should medicine become militant, crusading against and crushing those purposes that are antagonistic to health? Should it remain neutral, satisfied with restoring the conditions for purposeful freedom and accepting the ambiguous consequences? Quality medicine may improve quality of life by reviving the quality of purposefulness, impaired by ill-health. Can it or should it strive to promote quality of life, which requires defining and effecting good purposes in the social, economic and environmental world?

"Medicine, by reducing or eliminating the coercions of ill-health, serves human purposefulness."

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The State of Health and the Quality of Life

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HEALTH IS THE greatest of blessings, or so the saying goes. Throughout history, however, most people have behaved as if health was a less interesting topic than disease and its treatment. Among ancient people, the cults of Aesculapius and the other healing gods have always flourished more vigorously than the cults of Hygeia and the other deities identified with health. Among us, no painting has greater popular appeal than that of the doctor leaning over the bed of his patient; no article is more widely read than one describing a new disease, a new drug, a new surgical feat. Even the healthiest people love to discuss their physical ailments and emotional problems, or those of their acquaintances. Whereas disease contributes exciting elements to literature, the theater and the plastic arts, health inspires only cold official speeches and allegoric paintings that do not reach the human heart.

The popular fascination with medicine results of course from the fear of disease, but in part only. People are interested in disease because it brings to light aspects of human nature that remain concealed in the state of health; they see in medicine a scientific way to a richer and happier life. In theory, the role of the health professions is only to prevent or correct the disorders of the body and the mind; but in practice this role extends to many other aspects of life. The ideal family physician is expected to be a general counselor as well as a healer. In fact, there is an increasing tendency to assume that the medical profession can help individual patients and the community as a whole to achieve a higher quality of life—whatever this may mean.

"Whereas disease contributes exciting elements to literature, the theater and the plastic arts, health inspires only cold official speeches and allegoric paintings that do not reach the human heart."

I am of two minds concerning the view that the professional role of medicine should be enlarged to reach into more social fields. On the one hand, it is obvious that the health professions contribute to the quality of life not only through the management of disease but also through the creation of healthier environments. But on the other hand, it is certain that the quality of life involves value judgments that are highly subjective and that transcend medical formulation. Physicians—qua physicians—do not have special qualification to teach the art of life. When they provide useful guidance on this score, it is usually by virtue of their qualities as human beings rather than because of their scientific knowledge.

Some of the factors that contribute to the quality of life are common to all human beings; they are inscribed in the genetic code of the human species and probably have not changed significantly since the Stone Age. Civilized and sophisticated as we may be, we have inherited from our distant ancestors the ability to derive some of our most profound satisfactions from the activities of daily life—when we eat, drink and love; dream, tell stories or enact imaginings in gestures and pictures; participate in community events where we are both spectators and actors. Today, as in the past, young people crave for emotional and sexual love; old people long for quiet and comfort; people of all ages enjoy the very experience of living.

The phrase "joie de vivre" denotes those as-

Refer to: Dubos R: The state of health and the quality of life, *In* Medicine and the quality of life—A forum. West J Med 125:8-9, Jul 1976

pects of the quality of life that are biologically determined. Medicine can help human beings to experience them by seeing to it that the human biological machine is maintained in working order.

There are other aspects of the quality of life, however, that transcend the biological joie de vivre and that have a more personal basis. They are denoted by the word happiness, which always involves highly subjective cultural values. The determinants of happiness differ from social group to social group and indeed from person to person; although they loom large in the quality of life, they cannot be defined in orthodox medical terms.

The concept of health also has highly subjective connotations, precisely because it is conditioned by the personal view of happiness. To be healthy does not mean the same thing for a lumberjack in the Canadian Rockies and for an actor of the same age and size who has to perform every evening on a Broadway stage. A young woman who has elected a pioneering way of life in an Israeli kibbutz has requirements with regard to physical and mental health very different from those of another young woman who wants to achieve success as a fashion model in New York or in Paris.

"The concept of health also has highly subjective connotations, precisely because it is conditioned by the personal view of happiness."

The criteria of health, furthermore, change with time. The thickly fleshed Venuses of the late Stone Age differ from the ethereal 19th century heroines of Pre-Raphaelite paintings, not because feminine anatomy or physiology has changed, but because the criteria of sexual desirability are socially conditioned. There have been analogous changes in the criteria of masculine health. To be rather obese was considered socially desirable among the men of the Victorian era, but this is now considered biologically objectionable because obesity is associated with pathological conditions.

The quality of life depends also on the state of "public health"—namely on factors that affect the biological welfare of the community as a whole. Even in this public sense, however, the word health implies value judgments that transcend purely medical criteria. It is certain for example that societies can prosper economically under bad environmental conditions—murky skies, polluted rivers, little opportunity to experience the colorful pageantry of nature, the song of birds, the fragrance of flowers. Such environmental deprivation impoverishes life both biologically and spiritually, but is usually considered outside the province of medicine as long as it does not express itself in overt disease.

In many cases, however, environmental conditions that are tolerated by the general public because they do not immediately cause disease have consequences that are dangerous in the long run; the dangers may be of a medical, ecological or social nature. Experts, medical or otherwise, can often anticipate such long-range effects, but this does not entitle them to decide what courses of action will improve the quality of life. For example, the public may be less interested in environmental quality than in economic prosperity. Physicians cannot judge for society what its future should be; they can only warn it that environmental conditions are eventually reflected in the state of health and therefore in the quality of life.

Thus, medicine cannot by itself determine the quality of life. It can only help people to achieve the state of health that enables them to cultivate the art of life—but in their own way. This implies the ability to enjoy the fundamental satisfactions of the biological joie de vivre. It implies also the ability for each person to do what he wants to do and become what he wants to become, according to human values that transcend medical judgment.

Physician Responsibility and Patient Freedom

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WANDERING THROUGH the history of medicine one can find no period comparable to the present in which there has been so much concern about quality of life. Perhaps knowledge and resources were so limited in times past that physicians could do little more than try to grapple (often without coming to grips) with life and death situations. The only variable was the personality of the individual physician—a force not to be underestimated—since often it represented the only tool available.

But we have transcended this era. With our modern engines of survival we have forced the enemy death onto new unfamiliar terrain. Definitions of life and death are obscured. Diseases with predictable outcomes in the past must be reevaluated, for each day brings some new physiologic revelation. And this is prelude to the salvage of patients who would have died a few years back.

In this new environment the physician has changed. No longer is he a fusty mystical character who charmed and cajoled and scolded and prayed while dispensing his dreadful draughts and preposterous potions. He knew of his diagnostic and therapeutic impotence. It was a time of frustration for the conscientious; a heyday for charlatans.

"We have become a profession of optimists, and some among us feel there will be no limit to our ultimate power to heal."

It has only been a few generations since physicians have been given power over disease. And with this has come a change in philosophy. We have become a profession of optimists, and some among us feel there will be no limit to our ultimate power to heal. Most of us have become so smitten with this new capability that we have become zealots, missionaries, crusaders in the cause of health. I fear the pendulum has swung a bit far.

By the very nature of our calling, physicians are adversaries of the enemy death and its cohort disability. Our literature reflects this attitude. Until recently success in medicine was measured by objective remission or temporal survival, with scant attention to quality of life. It was inconceivable to most of us that anyone could place health and survival at a lower level of priority than security, money, pleasure, work or any other consideration. Yet, there always have been some persons who did just that.

So where does the physician draw the line? Where does *physician responsibility* end and *patient freedom* begin? What do you do with a patient who suffers the hellfire of recurring pancreatitis, yet continues to drink alcohol; a patient with chronic obstructive airways disease with recurring bouts of bronchitis, who continues to smoke cigarettes; a businessman with two previous myocardial infarctions, who continues to eat to excess, refuses to exercise and maintains a breakneck pace in his business?

Carry it one step further. How do you regard any motorist who refuses to wear a seatbelt, a motorcyclist who scorns a helmet or anyone who voluntarily jumps out of airplanes?

How about a patient with metastatic disease of the colon who makes the decision against chemotherapy? She prefers morphine—promethazine and a short life to more prolonged survival with hair loss, recurring oral ulcers, and the conse-

Refer to: Moser RH: Physician responsibility and patient freedom, *In* Medicine and the quality of life—A forum. West J Med 125:10-12, Jul 1976

quences of pancytopenia and compromised immunity.

Who is right? Should a physician refuse to take care of a patient who has a serious chronic illness that is amenable to palliation, yet who ignores advice which is predicated on years of clinical wisdom? How does one tread that line between professional obligation to the *patient* and respect for the integrity of a free, properly informed *human being?*

Too much permissiveness and we abdicate our classical role as a physician-parent, we leave many less sophisticated patients lost and bewildered. To many such persons the physician is still all-powerful—his word is gospel and his orders are to be followed absolutely. Such patients are childlike in their faith. They assume a fundamental integrity, a sense of responsibility on the part of a physician that is preeminent above all other considerations. They do not challenge; they do not question. They are rare.

Others accept the physician as a dedicated—but fallible—human being. They expect a reasonable explanation of diagnostic procedures and therapeutic interventions, and a reasonable prognostic guess. They will cooperate as intelligent, informed members of the therapeutic team. But they reserve the right to final judgment about selecting the quality of their life.

"I sometimes have the vision of medicine wielding a giant mold . . . . "

I believe we must not capitulate and yield to the caprice and whim of a frightened or panicky or ill-informed patient. Yet I do not believe we can impose our "crusade of good health" upon the patient. I sometimes have the vision of medicine wielding a giant mold—impressing it irrevocably upon patients—and attempting to stamp each patient according to our fixed concept of compliance to the "rules of good health." This approach fails to account for the enormous variation in individual goals, life-styles, desires, ambitions, self images.

There is a need for appropriate salesmanship as we attempt to convince a patient to accept a diagnostic procedure or a therapeutic manipulation that we are convinced is in his best interest. But in the same moment we must realize that there are still some patients who will disagree and make different decisions about what takes priority in their lives. They are listening to that different drummer, and one cannot command or legislate good health habits. Such things are alien to the spirit of free men.

We speak a great deal about bringing patients

into the therapeutic team—to ensure compliance with therapy. This is a new concept. In the past the almighty physician would make the diagnostic pronouncement and scribble an illegible Latinoid prescription, and the patient would depart—meekly accepting the talisman without question. The physician would take comfort in the delusion that since the patient "made the effort to come to see me, he will abide by my judgment and recommendations." It was considered as an article of medical faith. In most instances little effort was made to ensure comprehension and faithfulness in following instructions. It was rare for an explanation of the goals and hazards of therapy to accompany the magic slip of paper. Most often the transaction was an arbitrary monologue. And often failure of the patient to respond was related to the "inexorable course of the illness," with nary a thought that the patient might not even have purchased the medication.

Successful management of chronic diseases demands patient cooperation. Most patients are eager to learn about their disease, and many become intelligent partners in management. We have learned this lesson from patients with diabetes mellitus who can be taught to manipulate their insulin and diet on the basis of urine glucose analysis and early minor symptoms. We have learned from hypertensive patients who take blood pressure readings at home and are able to adjust their drug therapy accordingly. We have learned from patients with coronary heart disease who can be taught to exercise to specific limits of heart rate and anginal discomfort. All are examples of team management, and there are dozens of others.

The day has passed when we can declaim with thunder from Olympus, "I *know* what is best for you." On what basis do we judge a patient who opts for a short, pain-free, joyful (for him) life—rather than a longer road of discipline and discomfort. (I realize the options are rarely black or white, but I must confess I am not sure of my own reaction were I given the choice of an additional year or two of life with palliative cancer chemotherapy and its sequelae, or a trip to see the Taj Mahal by moonlight and the wonders of the Nile and other untasted delights, while aided by morphia.)

Certainly full disclosure measured to the intellectual and emotional capacity of the patient, with forthright recommendations—is the obligation of every physician. But we must respect the judgment of a patient who still elects to place priority on something other than health or longevity or even freedom from discomfort. I feel this philosophy represents a new plane in the evolution of the healing arts.

Unfulfilled Expectations

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GOOD HEALTH is a universal concern that is basic to the improvement of the quality of life. However, medicine's narrow popular definition which is often confined to the treatment of diseases and the delivery of health services has distorted its meaning both for the doctor himself as well as his patients. Such limited application has tended to denigrate the role of the doctor in improving the quality of life. The doctor finds himself in the contradictory position of probably having contributed more, as well as failed more, than almost any other professional to improve the quality of life of his fellow human beings. In my activities to increase the pool of persons who are being educated as health professionals, I am usually looking at the essential contributions of health professionals—especially doctors. Conversely, my concern for the recipients of health services via our health centers brings me face to

Refer to: Elam LC: Unfulfilled expectations, *In* Medicine and the quality of life—A forum. West J Med 125:12-14, Jul 1976

"The doctor finds himself in the contradictory position of probably having contributed more, as well as failed more, than almost any other professional to improve the quality of life of his fellow human beings."

face with the unrealized expectations of those who are not health delivery practitioners. It is my conclusion that both doctors and patients are deprived of a rich quality of life from two very different points of view.

The basic economic principle that the "haves" get more and the "have-nots" lose what they seem to have is of course operative. Within this context, the doctor has the capacity to enhance his personal potential for improved quality of life concomitant with the enhancement of the lives of his patients. This is usually the case. But despite this positive association, an awareness of loss potential may improve the doctor's contribution to quality in certain areas. Let me mention some of the disappointments or at least unfulfilled expectations that have implications toward what the quality of life is conceived to be.

The Black community has for a long time looked upon medicine as primarily concerned with improving the quality of life. Its practitioners are seen as having a responsibility to employ their knowledge and resources to improve the entire community. Hence much of the disappointment and resentment are related to unfulfilled expectations in this regard even in the face of great admiration for the profession's scientific progress in the delivery of health services. Persons suffering from the psychological and social pain inflicted upon them because they are Black or poor, or for some other reason, feel alienated from society, do not feel that they should also suffer physical pain. Their increased use of available health care is partly related to their search for a pain-free existence that compensates for psychosocial deprivation.

The poor have an additional expectation which is prompted by their view that the distribution of wealth is negatively affected on their behalf by the economics of health care. In view of this, they expect employment and other economic benefits from the health field. While the ostensive concern is over the inequitable distribution of health resources, at least a part of the concern is related to the possibility of jobs, training and community development. Medicine, having facilitated their search for a physically pain-free existence, is also called upon to bring relief to the total life situation.

Those persons, too, who live in relatively isolated areas such as rural areas have more expectations. They believe that the presence of a doctor, or a health facility, will add to their feeling of security—if they get sick, there will be someone to take care of them. The Black, the poor, the isolated and the socially disadvantaged expect a great deal more from medicine than a pill or an operation—they look to medicine as a means by which their entire life-style can be affected.

A physician, who thinks that it is enough to keep people healthy so that they can work, may have difficulty seeing these ancillary health benefits as primary interests. He may also find it difficult to understand the desire for a health facility in a neighborhood or village when there is a medical center in a nearby town. Or he may misunderstand a community that places the blame on the medical profession for the infant mortality rate or the pronounced incidence of obesity and malnutrition—all of which correlate with the economic life-style more than with the availability of health care. If these persons mentioned above are correct in their assessment that medicine could improve the quality of life for them, are they not also correct in their accusations that medicine is depriving them by not contributing more to improve their quality of life? A person's expectations and aspirations form the context in which he judges the quality of his life.

The quality of life in this society is closely associated with the development of an individual person's potential. One feels that his life is enhanced if he can perfect a new skill or excel in an established one that is marketable. He gains a deep sense of personal worth and satisfaction if life challenges his mental capacities and he is successful in addressing these challenges. Once the physical base of quality of life is within reach (good health), one's abilities and resources are utilized to attain those things which he associates with a higher quality of life.

A personal surplus of resources is regarded as indicating an excellent quality of life because it suggests that one is required to expend a limited amount of time acquiring the maximum resources and there is time left for the development of

one's potentials. Unfortunately, too often the surplus resources become the end rather than the means. The accumulation of surplus resources or conspicuous consumption may detract from the quality of life rather than add to it. As such, the field of medicine fails medical practitioners more than it does others in the enhancement of the quality of life, because the practice habits which demand long work hours, improper recreation, overcommitment in various projects and activities, and continuing education during off-time all conjoin to make a doctor's life less satisfying.

I conclude that whereas the medical field inevitably enhances the quality of life for practitioners and consumers in some important ways, it fails to fulfill the expectations of a number of consumer groups, and worst of all, it fails to enhance the quality of a doctor's own life to the degree possible. This failure is camouflaged by the accumulation of surplus resources (money and things) which become symbolic of a quality of life that does not in fact exist.

There are few solutions to this problem. Despite the warnings that an oversupply of practitioners faces us in the future, there is nevertheless the need to produce more well-trained persons. This will satisfy the demands of groups such as the poor and the minorities to utilize the apparent way of life of practitioners as a means by which they gain money, other resources, a challenge as well as status—and hence an improvement in the quality of life. If done properly, increased manpower production will also help practitioners whose lives are marred by a 70-hour work week or other factors that circumvent a richer life; for example, normal parental responsibilities or aesthetic enjoyment.

" . . . they look to medicine as a means by which their entire life-style can be affected."

An increase in health education would aid consumers to enhance rewards from medicine. All too often, the delay in seeking help robs a would-be patient of hours or days of pain-free existence. Improved public education about the potential health benefits of a visit to a doctor or health center may help many persons alter their conceptions of what is possible.

Perhaps the most important advances will come as physicians and other practitioners assume the role of transformers of life as a whole. In this light medicine will become a vital part of, not an adjunct to, a higher quality of life. The quality of life that should be sought is not that facilitated by excess or that accommodated to by deprivation, but that gained through the optimum utilization of resources indigenous to a given culture.

Limiting Assumptions

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MEDICAL STUDENTS (and the public for that matter) are exposed to a wide range of implicit messages regarding the determinants of health and the role of medicine in contemporary society. These messages are subtle but powerful. They help shape our beliefs about health and disease and to a large extent determine the direction of our medical effort, how we deploy health care resources, how we train health professionals, what we regard as valid subjects for research and how we regard our personal health-related behaviors. To highlight and make explicit these messages and their underlying assumptions one must often look beneath the rhetoric and token acknowledgments of alternative points of view.

For example, it is not uncommon for a lecture to begin with some brief comment to the effect that disease is the product of a complex host-agent-environment interaction. Then for the next three hours the specific agent of disease is discussed in minute detail along with the notable advances in chemotherapy aimed at this specific agent. Diseases are presented as specific entities, as events that "happen" to someone or as things that people "catch." Such is the enthusiasm of this discussion that the host and the complex of environmental determinants (physical and psychosocial) quickly fade into the background. Sometime later at the bedside or in the clinic the focus of attention becomes symptoms, physical findings and laboratory values. But what of the person? What of the human experience of illness? What of ethical questions? In practice, if not in theory, these concerns take a back seat to more technical concerns. Much of this is communicated implicitly.

"Diseases are presented as specific entities, as events that 'happen' to someone or as things that people 'catch.' "

At the risk of exaggerating and oversimplifying for purposes of illustration, I would like to make explicit some of these messages and assumptions that characterize much of modern medical practice.

First, health equals the absence of disease. This derives from the principal focus of medicine which is disease, its diagnosis, treatment and prevention.

Second, the best way to improve health is through medical care—that is, the treatment of those who are sick. The health of people is largely determined by and dependent upon the advances of modern medicine, the treatment of infectious diseases, the development of drugs and surgical procedures, and the construction of sophisticated hospital-based biomedical technology. The predominant model of contemporary medicine is the medical center where technological and professional resources are concentrated and applied to acutely ill persons on an episodic basis.

Third, scientific medicine equals the attempt to dissect the human organism into component parts in order to understand the mechanisms of disease. The assumption is that the human organism ultimately can be explained using physics and chemistry.

Fourth, the basic problems of human health and disease are essentially amenable to technical solutions.

Fifth, the physician is essentially responsible for the health of the patient.

Sixth, ancient, primitive, folk and unorthodox systems of medicine are archaic and of little relevance for contemporary medicine. At best they represent historical curiosities; at worst, impediments to medical progress. It is assumed that

Refer to: Sobel DS: Limiting assumptions, *In* Medicine and the quality of life—A forum. West J Med 125:15-16, Jul 1976

contemporary Western medicine has long ago surpassed these ancient practices, incorporating anything that was of value.

I could go on. The point is that even if we do not fully subscribe to the above views, we more often than not act as if they were true. Further, it is not so much that these views are wrong, but rather that they reflect a limited and incomplete conceptualization of health and medicine. They do not equip us to deal effectively with certain aspects of human health which for want of a better term we call the quality of life. The juxtaposition of medicine and the quality of life, however, invites the consideration of alternative points of view.

For example, when health is viewed as the quality of life rather than the absence of disease, the examination of the determinants of health that lie largely outside of the medical domain becomes more likely. While medical care certainly contributes to the quality of life, no one is likely to equate the absence of the signs and symptoms of disease with a life of high quality. Therefore, it is more probable that due attention is given to such factors as environmental quality, social support systems, psychological states, and individual behaviors and lifestyles as complementary strategies for improving health and the quality of living.

Physicochemical reductionism, useful though it may be, tends to limit our concern to those aspects of human health that can be measured using physics and chemistry. As a consequence of this quantitative focus, medicine has undervalued and overlooked those qualitative aspects of human experience not amenable to such analysis. As Abraham Maslow stated, "When the only tool you have is a hammer you tend to treat everything as if it were a nail." Further, the technological focus of contemporary medicine overshadows the fact that all medical decisions involve value judgments as well as clinical facts. The relationship between medicine and the quality of life demands that we consider the ethical dimensions of medicine and question the technological imperative that drives medical practitioners to intervene because they *can,* not because they *should.*

With regard to the responsibility for health, if one's view of the quality of life includes autonomy, self-determination and individual freedom, then the medical system should reflect these values. Health professionals should provide resources and information to help persons make informed choices regarding their health. The responsibility, in this view, is jointly shared. A medical system that fosters dependency and undermines an individual person's confidence is clearly counterproductive to this ideal of individual freedom.

" . . . to reevaluate some of the ancient and traditional systems of healing in light of contemporary health needs."

Last, a consideration of the quality of life and medicine may permit us to reevaluate some of the ancient and traditional systems of healing in light of contemporary health needs.[1] Many of these systems contain approaches aimed not only at the treatment of disease but at the provision of meaning for the experience of illness and death. Further, they contain valuable perspectives on the ecological relationships that govern health as well as techniques to enhance self-regulation of internal physiological and mental states. In short, a serious examination of ancient and alternative systems of medicine may serve to complement and extend contemporary scientific medicine, not only in the treatment of disease but in improving the total quality of living.

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Benjamin Rush and the Beginnings of American Medicine

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I

When the first permanent European colonies were established in North America in the early decades of the 17th century, the European settlers faced a trackless wilderness sparsely populated by nomadic people, the Indians. The pioneers had left behind a complex European civilization of cities, cathedrals, universities, medical schools and hospitals. In their new homeland they encountered almost unbelievable hardships and dangers.

One especially serious privation was the absence of physicians to whom they could turn confidently when beset by the severe illnesses that were prevalent among them. It is true that at that time even the best physicians in their native countries were powerless against most diseases. But the patients had the comfort and peace of mind of being treated according to the accepted and traditional methods.

The Pilgrims in New England were more fortunate than the colonists in Virginia, for they were a more deeply religious people, with complete faith in the Lord. Secure in their belief and sustained by the promise of salvation, they put their trust in His divine mercy and accepted illness and death unquestioningly as His will.

The trials and hazards of the colonists began long before their ships reached the shores of America. In this day of jet air travel, it is difficult to imagine what the crossing entailed when our forefathers began their westward migration. Their small sailing vessels were crowded and unclean; the food was bad, and the sanitary conditions most primitive.

The journeys took as long as six months, and on every crossing many passengers became ill and died. They were so weakened by scurvy, from lack of fresh foods; and by seasickness that they could not resist infections. If contagious disease broke out, as it usually did, there was no way to isolate the sick; and the illness became rampant. Even if a physician was aboard, he could do little to halt the spread. On some voyages most of the passengers, officers and crew perished before land was reached.

After landing in the New World, the hardships became even greater. Desperate homesickness and a wild land with extremes of temperatures, inadequate shelter, starvation, backbreaking labor, unfamiliar diseases and hostile Indians created miseries beyond description. The death rate, particularly among the children, was appalling. These first settlers needed great courage and fortitude in order to survive and establish homes and communities.

The lack of professional medical care persisted for a long time and was only gradually overcome. Ship doctors sometimes stayed for a year or two before returning to Europe. Occasionally physicians came as immigrants, but they were too few to influence the medical scene of the colonies. Furthermore, one colony was often too distant from the next settlement to be reached in time, even if a doctor were available there.

Under these circumstances the care of the sick became the task of colonial leaders—the gover-

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nors, the clergymen and occasionally school teachers—all of whom had had more education than the rest. The Reverend Samuel Fuller, for instance, who arrived on the *Mayflower,* had attended lectures on medicine while he lived in the Netherlands. Although he was not a physician, he served as one until his death in 1633.

Governor John Endecott of the Salem settlement (1589-1665) took over the responsibility of providing medical advice to his people, as did John Winthrop of Boston and his son, who succeeded him. The elder Winthrop sent a doctor friend in England an inquiry about what to do in the case of sickness. The doctor responded with a long letter containing instructions for the treatment of various illnesses. Winthrop's son conducted a great deal of medical practice by correspondence. The first medical publication in colonial America was a pamphlet on the care of smallpox and measles, written in 1677 by a preacher, Thomas Thacher, and addressed to the people themselves.

The task of nursing the sick fell, of course, to the women, many of whom were quite competent. The delivery of babies was likewise entrusted to women. Some had received training and experience as midwives before their migration.

As time went on, the colonial population increased; better homes were built, and living became easier. Doctors began to join the colonies, and sons of the settlers started to study medicine by serving as apprentices to the physicians in practice. Some of them finished their training by traveling to Europe for study in the medical centers on the continent, but more went to Edinburgh or London, where there was no language barrier to overcome. Even after schools and colleges had been established in the colonies, the graduates who wished to become doctors usually received their medical training in the Old World.

II

Infections played a much greater role in illnesses at that time then they do today. Many diseases that have since been almost entirely eliminated were raging in full fury. Serious diseases swept over the entire world. The American colonies were not spared, although the sparseness of the population did not lend as much fuel to the epidemics as did the overcrowded European cities and rural districts. If the doctors in the centers of learning were powerless to cope with these epidemics, what could be expected of the handful of scantily trained and poorly equipped doctors in the New World settlements?

Of all the dread diseases, smallpox was the most widespread and deadly. Those who survived it were usually disfigured by permanent scars. Early in the second millennium A.D., however, the first steps in the prevention of this disease were taken in the countries of the Far East and the eastern Mediterranean.

Children in China and in the Near East were deliberately infected with a small amount of pus from a smallpox patient. A mild attack of the disease usually occurred but the children recovered with a few pockmarks only and were afterward immune to the infection. This process of introducing a disease into the body to produce immunity, known as inoculation, was brought to England in 1721 by Lady Wortley Montagu, wife of the British ambassador to Turkey, and was gradually adopted. In the same year a Boston clergyman named Cotton Mather read about the success of this method and persuaded a friend of his, Dr. Zabdiel Boylston, to try it. The experiment was a striking success.

Inoculation aroused a great deal of opposition from some physicians, but its value was confirmed in a number of epidemics. Thereafter it became widely used.

Benjamin Franklin who was interested in many medical and public health problems, at first opposed but later energetically supported inoculation. His influence was important in overcoming resistance to inoculation. These efforts were made more than a century before Edward Jenner, a small-town English doctor, carried out the first vaccination, inoculation with a very mild virus disease called cowpox (or *vaccinia,* from the Latin *vacca,* "cow") to confer immunity against smallpox. This form of inoculation has almost entirely freed the world from the dreadful scourge of smallpox.

The growing hostilities between the English colonies and their mother country resulted in the War for Independence. By this time the colonies, though still widely separated, had formed a loose organization, or confederation. Their people, no matter what their national origins had been, were all subjects of England. During the 150 years of development, the colonists had grown in number and had gathered enough strength and confidence to challenge the authority of Britain, the most powerful nation of the world at that time.

Medical care had also improved. Although

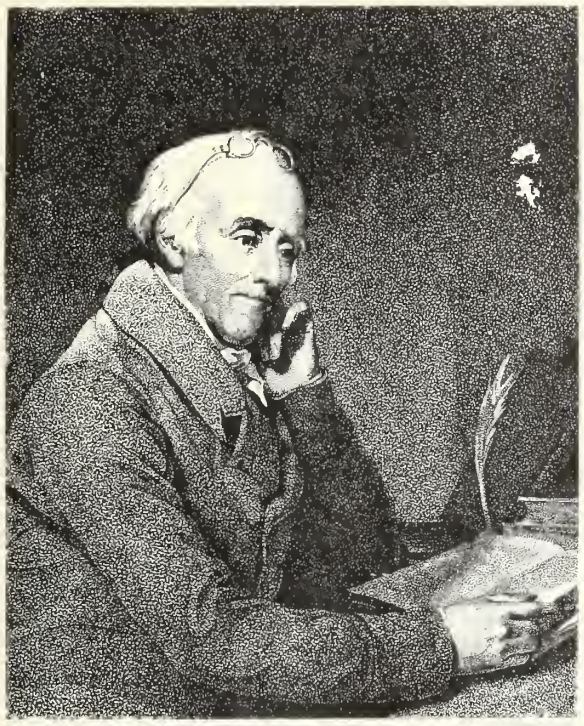


Figure 1.—Benjamin Rush, MD.

there were still no medical schools, the number of competent, practicing physicians was sufficient for the peacetime needs of the people. In some colonies, laws had been passed restricting the right to practice medicine to those who had been adequately trained and who had proved their competence by passing examinations. To prevent epidemics, quarantine regulations against contagious diseases had been established. The first colonial hospital was opened in Philadelphia in 1752 with the support of Benjamin Franklin.

Philadelphia, then the largest and most important city in the colonies, had also become the leading medical center. Most of the pioneer physicians whose names are important in the early history of American medicine were Philadelphians. One of them, William Shippen, Jr., learned medicine from his father and then spent five years abroad completing an excellent education. He studied with the great doctors in Edinburgh and London. On his return to Philadelphia in 1762, he began giving private lectures in anatomy, surgery, and obstetrics (concerned with caring for women before, during and after childbirth).

John Morgan, who had served his medical apprenticeship with a prominent Philadelphia physician, became a pupil of the famous Hunter brothers, William and John, in London. He then spent two years at the University of Edinburgh, which then had the best medical school in Britain, and visited the important clinics of France and Italy. After five years of study and travel, he returned to Philadelphia with diplomas and memberships in learned societies. But more important, he brought back the resolve to establish a medical school in Pennsylvania similar to the best in Europe.

Institutions of higher learning already existed in the American colonies. Harvard University had been founded in 1636, and there were others, including the College of Philadelphia, founded in 1740. It was in connection with this college that John Morgan and William Shippen established the first American medical school in 1765.

Four years later the versatile Benjamin Rush (Figure 1) joined the faculty. Since 1791, when the college became connected with the University of Pennsylvania, it has continued to play a very important part in American medical education. Other schools of medicine rapidly evolved on the eastern seaboard: King's College, New York, (later the medical faculty of Columbia University) in 1767; Harvard University, Cambridge, Massachusetts, in 1782; and Dartmouth College, Hanover, New Hampshire, in 1798.

When the American Revolution broke out in 1775, the colonies were not prepared. The situation was particularly serious in the army's medical services. Large numbers of doctors volunteered for both medical and military duty, and many gave their lives to the cause of freedom. However, there was no organized medical department.

Dr. Benjamin Church of Boston was appointed Surgeon General, but for various reasons, chiefly personal, he was soon replaced by John Morgan, who filled the office with tireless zeal. Unfortunately, conflicting authorities, politics, numerous complaints and a network of intrigue resulted in personal bitterness, broken friendships and a succession of four surgeons general before the war ended in 1781.

Morgan was dismissed, and Dr. Shippen appointed in his place. The discharge deeply hurt and permanently embittered Morgan. He blamed Shippen for plotting to bring it about. After submitting a report defending his conduct and performance of duties, he was cleared by Congress. Shippen, in turn, was court-martialed on com-

plaints made for the most part by Morgan and Benjamin Rush. Although he too was cleared, the stigma to his reputation persisted.

Health conditions in the Continental Army were deplorable. Clothing, housing and food supplies were poor, and there were no hygienic measures because their importance for disease prevention was not known. Of the many illnesses that attacked the troops, typhus was the deadliest. As typhus germs are carried by the body louse, the disease became an epidemic with a high mortality rate wherever people were crowded together in filthy surroundings as in camps, jails or ships. Serious as it was, typhus was but one of a number of illnesses that wasted the strength and took the lives of the officers and men in the Continental Army.

One bright note was the partial control of smallpox. Inoculation was very widely used. In fact, Commander-in-Chief George Washington ordered that all Continental Army troops be inoculated. There are no accurate statistics on the results of this measure, but in the northern campaign, according to General Horatio Gates, Commander of the Army of the North, smallpox was "perfectly removed from the Army."

III

The history of American medicine actually begins with the War of Independence, and the doctors whose names have already been mentioned became its leading figures. During the war feelings ran high against the Tories. One result was that in 1779 the College of Philadelphia, whose faculty was suspected of Tory leanings, was suppressed; and a new institution, called the University of the State of Pennsylvania was established.

Most of the faculty of the original college refused to join the new school. Later, in 1783, Benjamin Franklin and a group of other influential men succeeded in having the college reopened. All of the former faculty members were then invited to resume their positions.

Rush and Morgan, still harboring the bitterness of their war-time feud with Shippen, refused to return unless he was excluded. The college's board of trustees would not do this, and Rush and Morgan relented. The three former colleagues were together again.

There existed, then, two medical schools in the same city. This seemed unnecessary, and in 1791, they were combined in the University of Pennsylvania. (Morgan, however, who had never recovered from his resentment at having been removed from the office of surgeon general, withdrew from all public activity and died a broken dispirited man.)

With the combination of the two schools, Benjamin Rush received the professorship of theoretical and practical medicine, a position he filled with distinction for many years. (And it is to be noted that in 1806 he cared for Shippen in his last illness.)

The story of colonial medicine in North America is that of the gradual acquisition of enough doctors to meet the desperate need. Only limited training facilities were available; and with the pressure of practical duties, it was not to be expected that outstanding personalities could develop or that important medical discoveries could be made. However, in the postwar period, after the Revolutionary War, matters were different. The people became a nation and advanced in various professional fields. Very soon medical history began to be made in the United States of America.

IV

Certainly the most important medical figure in the young country was Benjamin Rush. The first American to attain medical prominence, he pioneered in medical education in the New World and fought for reforms in teaching and in treatment of the insane. He was a productive medical writer and a master of clear, graceful expression.

He wrote a number of important books, including his *Account of the Bilious Remitting Yellow Fever as it Appeared in the City of Philadelphia in the Year 1793,* outstanding for its graphic description of the disease. The book was based on his experience in treating more than one hundred yellow fever patients daily—until he himself became a victim of the disease. He also translated into English and annotated the Latin works of Sydenham, the famous English clinician of the previous century (see Figure 2).

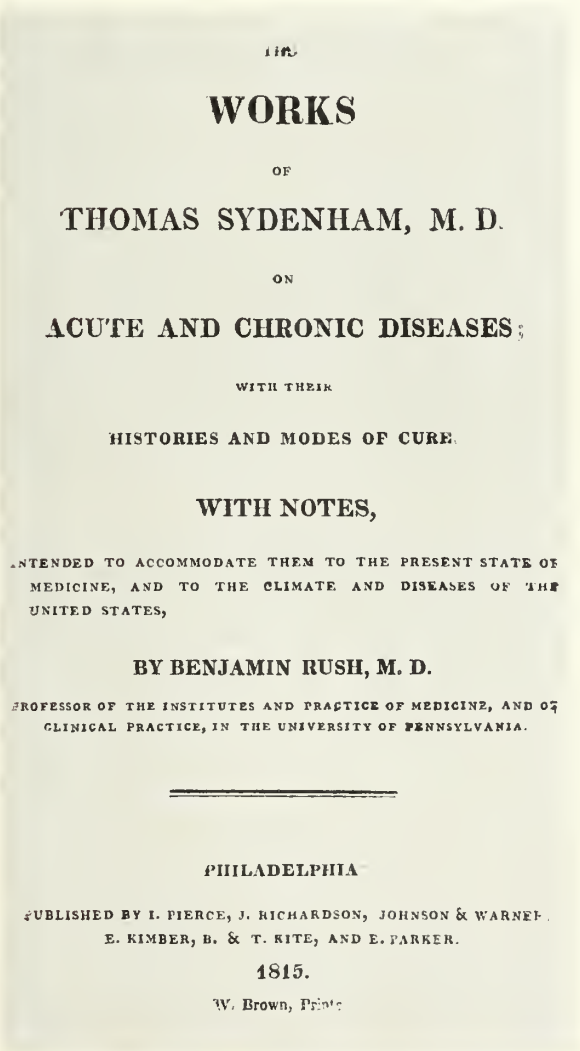
But Rush's medical activities were matched by his equally varied political interests and his crusading zeal for social and government reforms. Some of the movements he promoted were radical for their time and caused him some temporary loss of standing.

His family background and youth hardly pointed to his exciting life. He was born on his father's farm near Philadelphia in 1745 and was brought up a Quaker. His father and grandfather

had been gunsmiths as well as farmers. Benjamin Rush must have been a brilliant as well as an industrious student, for he graduated from Princeton at the age of 15.

Rush began his medical education as an apprentice for six years under a well-known physician, Dr. John Redman. Although this apprenticeship would have qualified him to practice medicine in the American colonies, his desire for a more formal medical education led him to Edinburgh, where he received his MD degree in 1767, and subsequently to London. A tour of medical establishments in Continental Europe, particularly in France, concluded the most complete medical training then available.

Immediately upon his return to Philadelphia in 1769, Dr. Rush accepted the professorship of medicine offered by the College of Philadelphia. When the college became part of the University of Pennsylvania, he retained this position. He also became a very successful practitioner and might well have confined his energies to the practice and teaching of medicine.



THE

WORKS

OF

THOMAS SYDENHAM, M. D.

ON

ACUTE AND CHRONIC DISEASES;

WITH THEIR

HISTORIES AND MODES OF CURE.

WITH NOTES,

INTENDED TO ACCOMMODATE THEM TO THE PRESENT STATE OF MEDICINE, AND TO THE CLIMATE AND DISEASES OF THE UNITED STATES,

BY BENJAMIN RUSH, M. D.

PROFESSOR OF THE INSTITUTES AND PRACTICE OF MEDICINE, AND OF CLINICAL PRACTICE, IN THE UNIVERSITY OF PENNSYLVANIA.

PHILADELPHIA

PUBLISHED BY I. PIERCE, J. RICHARDSON, JOHNSON & WARNER, E. KIMBER, B. & T. KITE, AND E. PARKER.

1815.

W. Brown, Print.

Figure 2.—Title page of Benjamin Rush's translation and annotation of the Latin works of the famous 17th century English clinician Thomas Sydenham.

The American Revolution, however, provided him with his first "cause." Before the outbreak of hostilities he took part in the political developments and became a member of the Continental Congress. Although only 30 years old, he was the most distinguished of four physicians who signed the Declaration of Independence. (The other three were Lyman Hall, Josiah Bartlett and Matthew Thornton.) From then on he never ceased to work for the improvement of the new republic. In the revolutionary army he served by congressional appointment as physician in chief, but only briefly. He was not supported by Congress and military authorities, including General George Washington, in his criticism of the medical department which was under the direction of another Philadelphia physician, Dr. William Shippen.

Dismayed by the dissension in the Army, Dr. Rush returned to Philadelphia to resume his medical career. When hostilities ceased, his freshly aroused political and social conscience drove him to lend his pen and his fervor to every reform movement that came to his attention. Although he was greatly interested in statesmanship and diplomacy, he was everything but a diplomat. That this won him as many enemies as friends may be readily understood, and the allegation on the part of his enemies that he might be a radical deterred Columbia College (later the Medical College of Columbia University) from offering him a position. Some of the causes he espoused seemed radical indeed. He was in violent opposition to slavery and became president of the Abolitionist Society of America. He spoke and wrote on prison reforms and became a leading member of the Philadelphia Society for Alleviating the Miseries of Public Prisons, and he advocated with fervor the establishment of free public schools for the poor, and for higher education of women. All of his writings reveal his broad educational background, his irreproachable logic, his flair for succinct expression and his gift for acrid satire. It need hardly be emphasized that these gifts did not add to his popularity. Thus, in 1787, when expressing himself "On the Defects of

the Confederation," he presented views which still today are the subject of frequent discussion:

> "The custom of turning men out of power or office, as soon as they are qualified for it, has been found to be as absurd in practice, as it is virtuous in speculation. It contradicts our habits and opinions in every other transaction of life. Do we dismiss a general—a physician—or even a domestic as soon as they have acquired knowledge enough to be useful to us, for the sake of increasing the number of able generals—skilful physicians—and faithful servants? We do not. Government is a science; and can never be perfected in America, until we encourage men to devote not only three years, but their whole lives to it. I believe the principal reason why so many men of abilities object to serving in Congress, is owing to their not thinking it worth while to spend three years in acquiring a profession which their country immediately afterwards forbids them to follow."*

The reason for this shortcoming he attributed to the total rejection of all things British: "We detested the British name, and unfortunately refused to copy some things in the administration of justice and power, which have made it the admiration and envy of the world." Among the British institutions that Rush deemed worthy of emulation was the preparation of government officials and diplomats. To remedy the situation in the newly founded United States, he suggested that Congress "instead of laying out half a million dollars in building a federal town, appropriate only a fourth of that sum, in founding a federal university. In this university, let everything connected with government, such as history—the law of nature and nations—the civil law—the municipal law of our country—and the principles of commerce, be taught by competent professors." In addition to these and many other subjects, the students were to be taught a superior command of English and at least two, but preferably three, foreign languages. Only thus, he felt, could statesmen be trained who would measure up to those of foreign nations. The following passage from a *Plan of a Federal University* (1788) despite its use of somewhat extreme expression, does contain a great deal of wisdom.

> "In thirty years after this university is established, let an act of Congress be passed to prevent any person being chosen or appointed into power or office, who has not taken a degree in the federal university. We require certain qualifications in lawyers, physicians and clergymen, before we commit our property, our lives or our souls to their care. We even refuse to commit the charge of a ship to a pilot, who cannot produce a certificate of his education and knowledge in his business. Why then should we commit our country, which includes liberty, property, life, wives and children to men who cannot produce vouchers of their qualifications for the important trust? We are restrained from injuring ourselves by employing quacks in law; why should we not be restrained in like maner, by law, from employing quacks in government?"†

In spite of his Quaker upbringing, Rush had supported the cause of the American Revolution. But he also believed that "his" war was to be the last one, the war to end all wars. He soon learned that wars were to continue and for reasons of which he could not approve. The United States was at war with the American Indians; the British fought with Tippoo Sahib, the Sultan of Mysore, in India; the planters of Santo Domingo fought against their African slaves, and the Germans battled with the French. To terminate forever all wars, at least so far as this country was concerned, he submitted "A Plan for a Peace Office for the United States." About this extraordinary institution he said:

> "It is to be hoped that no objection will be made to the establishment of such an office, while we are engaged in a war with the Indians, for as the War-Office of the United States was established in the time of peace, it is equally reasonable that a Peace-Office should be established in the time of war."‡

To engage in all his reform efforts, Rush had to be a man of boundless energy. This was true especially since his deep emotional involvement in the causes mentioned was only secondary—his primary interest was medicine. But in medicine, too, he found wide range for his reforming zeal. In establishing the first free dispensary in the United States, in Philadelphia (1785), he linked

*From Rush's "On the defects of the confederation," *In* Rush B: Inquiries and Observations. Philadelphia, 1787, *quoted in* Runes DD (Ed): The Selected Writings of Benjamin Rush. New York, Philosophical Library, 1947, p 28.

†From Rush's "Plan of a federal university," *In* Rush B: Inquiries and Observations. Philadelphia 1788, as quoted in *loc. cit.* pp 101-105.

‡From Benjamin Rush's "A plan of a peace-office for the United States, Philadelphia 1799," as quoted in *loc. cit.* p 19.

his two major interests, medicine and social reform.

The excellence of his medical training, to say nothing of the glamour of his foreign diploma, his solicitous interest in the welfare of his patients, and his diligence and punctuality in attending them, soon brought him the most enviable practice of his day. He was a pioneer in the clinical description of disease forms, motivated by an acute scientific curiosity. His therapy, on the other hand, was not only traditional, but he carried the use of bleeding and purgation to absurd extremes. He was thus inclined to enfeeble the patients on whom he lavished so much devotion and clinical attention.

Rush's therapeutic dogmatism was, however, of a minor proportion in his teaching, which was superb according to the opinions of his contemporaries, accordingly the quality of his printed lectures, and the number of his students, which is estimated to have exceeded 2,200 in the course of forty years.

Rush's teachings went far beyond the immediate student-professor communication. Through the medium of his writings, he reached an infinnitely wider sphere. The volume of *Introductory Lectures* (1811) and the four volumes of *Medical Inquiries and Observations* (1809) (Figure 3) reveal such a multitude of interest and such a wealth of information that it is easy to see why Rush was so highly regarded as a medical educator.

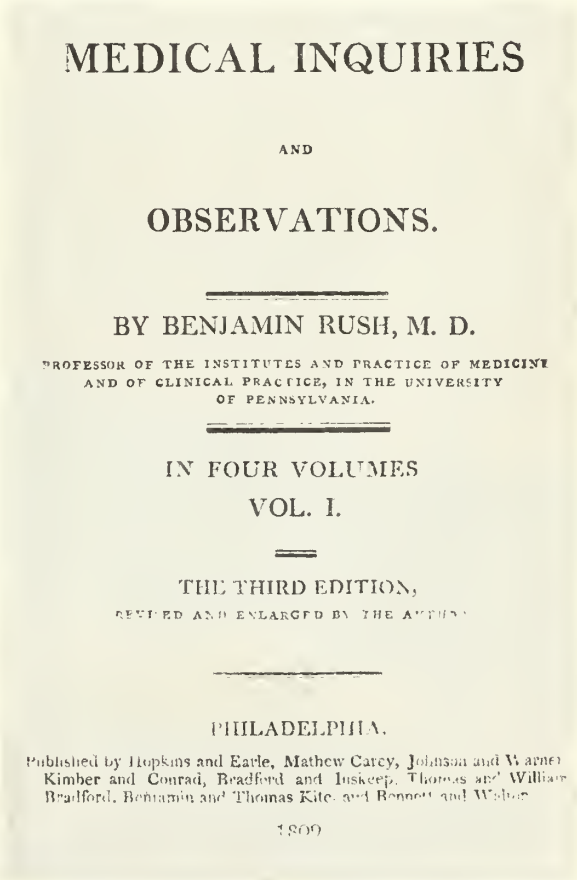
V

In addition to actual clinical information, he was most anxious to impart to his students the ethics of a good physician. Of particular interest is the lecture entitled "On the Means of Acquiring Business, and the Causes which Prevent the Acquisition, and Occasion the Loss of It, in the Profession of Medicine," which, despite its contemporary verbiage, is equally pertinent today. According to Rush, there were three ways of building up a good practice: first, by honorable means; second, by artificial and accidental means, and third, by dishonorable means.

The honorable means were relatively few. They included an ever-broadening medical knowledge, excellent manners, sympathy with the sick, attendance upon the poor, respect for religion, the publication of useful medical books and especially "punctuality in visiting patients and fidelity in complying with engagements." It is amusing that he also advises the novice in practice to familiarize himself with surgical procedures, for "the cures which are thus performed by him are so beneficial and obvious, and generally so magnified, as to become a kind of hot bed of a young physician's business and fame."

In discussing the much more numerous artificial and accidental methods of acquiring business, Rush reveals his sarcastic side as well as an incisive awareness of the baser motivations of his fellow men. Among these he counted patronage of all types, even including that of an old physician and a religious society. With reference to the last he wrote: "Dr. [Richard] Mead owed his introduction into business to the influence of a dissenting congregation in London, of which his father was minister.* Sir John Hawkins tells us he made it a practice, when his son was called

*Dr. Richard Mead (1673-1754) of London, an eminent and extremely wealthy physician of London, was highly regarded and exercised a great influence on the medical world of his day. In all probability he owed his distinguished position in English medicine less to his father's help than to hs own important publications and excellence as a physician.



MEDICAL INQUIRIES

AND

OBSERVATIONS.

BY BENJAMIN RUSH, M. D.

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IN FOUR VOLUMES

VOL. I.

THE THIRD EDITION,

REVISED AND ENLARGED BY THE AUTHOR.

PHILADELPHIA.

Published by Hopkins and Earle, Mathew Carey, Johnson and Warner, Kimber and Conrad, Bradford and Inskeep, Thomas and William Bradford, Benjamin and Thomas Kite, and Bennett and Walton.

1809.

Figure 3.—Title page from *Medical Inquiries and Observations,* a four volume work that helped establish Benjamin Rush as a great medical educator.

out of church, always to pray publicly for the recovery of the patient he was sent for to visit, by which means he enlisted religious prejudices in his favour." Benjamin Rush was offended by the success of "such ruses and tricks on the part of physicians simply for the pursuit of fame and monetary gain."

But above all, Rush distrusted all deviations from ordinary conduct which he considered dishonest affectations. Among these he listed: "Singularity in behaviour, dress, and diet. Great taciturnity, a sententious mode of conversing or the practice of nodding, instead of speaking in company. . . . Eccentricity of manners and conduct . . . [and] Great minuteness in inquiring into the symptoms of diseases. The inspection of the lips and teeth by a magnifying glass, the tasting of urine and sweats, the smelling of the faeces, and even getting into bed with sick people in order to discover the quality of their perspiration, have all been practiced with success as the means of acquiring reputation and business in medicine." Among his further annoyances were: "Trifling and absurd refinements in the prescriptions of medicine as to dose, manner of preparation . . . [and] An Affection of a sudden and intuitive knowledge of a patient's case by feeling but a few strokes of his pulse, or by barely inspecting his countenance. . . . "

The clearly dishonorable methods of building up a large practice are by far fewer and include: "Opposing the principles, and traducing the practice and characters, of brother physicians . . . Traducing new and popular remedies . . . [while] performing great and sudden cures, by some of those remedies in disguised form . . . Taking undue advantages of brother physicians in consultations, by extraordinary degrees of attention to their patients, neglecting at the same time their duty to their own. Publishing accounts of cases that never existed, and of cures that have never been performed. Charging fees so low as to allure patients from their old and habitual physicians. Flattering the prejudices of cities, and countries upon the subject of their health and their prosperity. . . . "*

In reference to this last-mentioned, Rush spoke from bitter experience. Some time before delivering this lecture, he had failed to flatter the prejudices of his city and had thus incurred the wrath of his medical colleagues, and eventually even the desertion of his patients. This loss of practice was the direct result of his unpopular stand in the numerous yellow fever epidemics, the first and severest of which struck Philadelphia in 1793. In searching for the cause of the epidemic, he noticed the greatest incidence of disease near the harbor, and upon finding a great quantity of rotting coffee on a wharf "Which had putrefied to the great annoyance of the whole neighborhood," he "was soon able to trace all the cases of fever . . . to this source." These conclusions were investigated further by the "Inspector of Sickly Vessels," who concurred in Rush's opinion and enumerated "in addition to the damaged coffee, some putrid hides, and putrid animal and vegetable substances, as the supposed cause of the fever and concluded by saying, as he had not heard of any foreigners or sailors infected, nor of its being found in any lodging-houses, that 'it was not an imported disease.' "

By thus throwing the onus for the epidemic upon the unsanitary conditions of the city and even advertising a warning to this effect in a Philadelphia newspaper, Rush heaped upon himself the ire of his fellow citizens. His medical colleagues joined his detractors, for "the sudden encrease of my business and the public effusions of gratitude from many persons who ascribed the preservation of their lives to my remedies, produced fresh acts of hostility against me."

Eventually, Rush was attacked in the newspapers. "Their design proved successful. They lessened my business, and they abstracted so much of the confidence of my patients as to render my practice extremely difficult and disagreeable among them. To put a stop to their injurious effects upon my business and the lives of my patients, I commenced civil action against . . . the printers." After having won his suit, he gave the $5,000 awarded to him by the law to the poor. Nevertheless, the publicity attendant upon the lawsuit and the active detractions of the other physicians had by 1797 reduced his practice below the point where it could support him and his family. To supplement his diminished income, a close friend successfully applied in his behalf to President Adams for the office of Treasurer of the Mint, which had just become vacant.

With his livelihood thus assured, Rush gave his remaining time to lecturing and writing and to service to the mentally ill at the Pennsylvania

*Observations on the Duties of a Physician and the Methods of Improving Medicine, Delivered at the University, at the conclusion of a course of lectures upon chemistry and the practice of physic. Published at the request of the class, *In* Rush B: Medical Inquiries and Observations, Vol 1, Third Ed. Philadelphia, Hopkins & Earle, 1809, p 435 ff.

Hospital. The variety of subjects which he covered in his books in addition to his work on psychiatry and his various accounts of yellow fever is too extensive even for a listing of titles. Of special importance, however, are his descriptions, which are among the earliest, of cholera infantum and dengue and his recognition of thermal fever, believed to be occasioned by drinking hot water when overheated. He was also the first to raise the question of focal infection in an "Account of the Cure of Several Diseases by the Extraction of Decayed Teeth." His medical interests went far beyond the clinical subjects. He delved into the eternal question of the cause of life, and he wrote on military medicine and hygiene. He even made the first American contribution to anthropology in his study on the German inhabitants of Pennsylvania and his penetrating inquiry into the history of medicine of the North American Indians and the "comparative view of their diseases and remedies with those of civilized nations."

VI

Rush's contributions to psychiatry were made after his election as physician to the Pennsylvania Hospital in 1783. This hospital (Figure 4) had been founded some 30 years earlier for "the cure and treatment of lunaticks" in order that "they may be restored to reason and become useful members of the community." The harsh treatment then given to the "lunaticks" was hardly likely to restore them to health. The patients were kept in filthy cells that had no heat. Humidity, rodents and insects bothered the patients as much as the cold.

Rush studied the situation for several years and then began his criticism of the aimless treatment and bad housing of the patients. In 1789 he addressed the hospital's board of managers, requesting improvement in the sanitation of the patients' quarters and, more important, the opportunity for employment "for such of the Deranged people as are Capable of Working." Simple as these reforms may appear, they were then entirely new ideas in the treatment of mental diseases in the United States.

According to Morton's *History of the Pennsylvania Hospital,* the active treatment, originally given to the "lunaticks," was hardly suited to restore them to health. The patients were subjected to alternate torrents of hot and cold water, "their scalps were shaved and blistered, they were bled to the point of syncope; purged until the alimentary canal failed to yield anything but mucus, and in the intervals they were chained by the waist, or the ankle to the cell wall." The cells themselves were filthy, totally without provisions for their heating and located on the ground floor of the building where crowds of spectators had easy access to the cell windows and could watch the antics of the inmates. To check this "Disturbance given to Lunatiks" a palisade fence was erected in front of the windows which was, however, insufficient to keep the crowds away. Even the injunction issued in 1762 that such "persons who come out of curiosity to visit the house

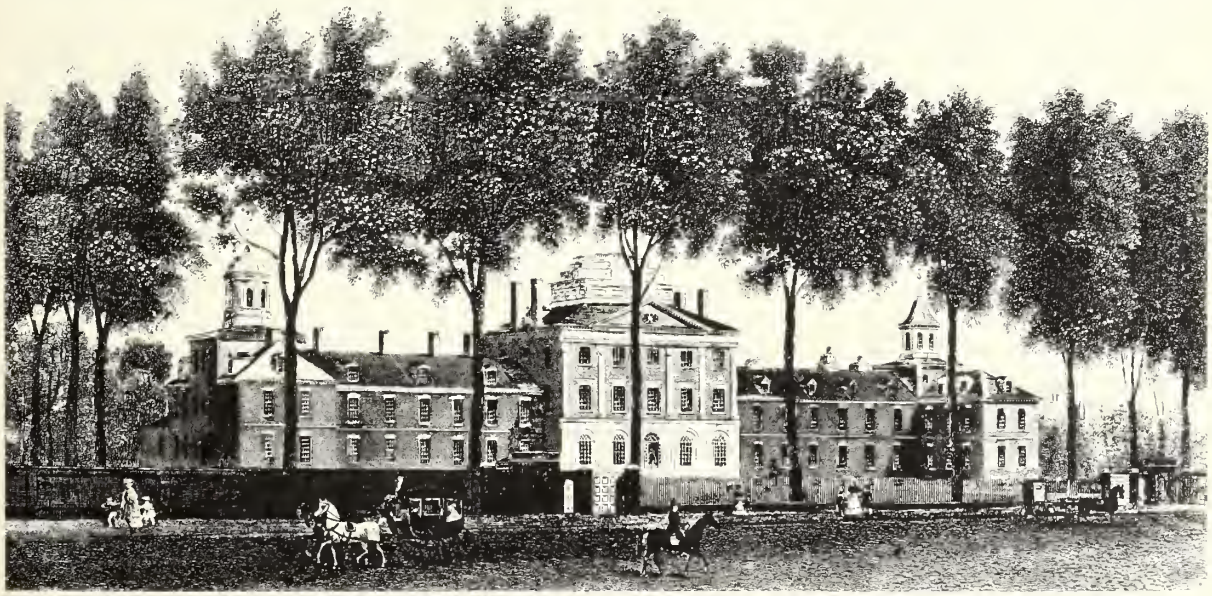

Figure 4.—Pennsylvania Hospital, Philadelphia, founded for "the cure and treatment of lunaticks."

should pay a sum of money . . . for admittance" did not prove to be a deterrent to the curious.

It was extremely easy to commit a patient to the hospital; relatives, friends or neighbors simply had to sign a paper and apply for admission to the managers; the patient was left without appeal. Indigent patients were accepted free of charge, for others the custodians had to place bond to take care of board and funeral expenses should the patient die while in treatment. After several years of silent observation, Rush began his vocal intercession against the aimless treatment and bad housing of the patients.

Rush's opinions were so deeply respected that the board immediately resolved to change existing conditions. He suggested further reforms concerned with the finding of suitable persons to care for patients. Dr. Benjamin Rush's major reforms in psychiatry changed the prospect for the mentally ill in America from a future of unrelieved neglect and decline to one of possible improvement and even cure.

His concern with even the lowliest aspects of his patients' well-being is emphasized by his further recommendation that the cells be furnished with mattresses and chairs and above all that the open chamber pots be replaced by "closed stools with a pan half filled with water to absorb the foetor from their evacuations." In contrast to his contemporaries Rush was certain that "degraded as the patients are by their disease, a sense of corporal pleasure, of joy, of gratitude, or neglect and injustice is seldom totally obliterated from their minds."

Benjamin Rush's interest in mental diseases was not confined to his ministrations at the Pennsylvania Hospital. It found expression in his writings and his lectures. To him, the study of the mind was an indispensible part of the general field of medicine and his recommendation of its adoption into the medical curriculum has lost little of its early pertinence.

VII

The essence of his psychiatric thinking Rush assembled in an important volume entitled *Medical Inquiries and Observations upon the Diseases of Mind* (1812). This book and an earlier article on the "Influence of Physical Causes upon the Moral Faculties" are the first and for many decades the only American publications on the subject of mental disease from its severest psychotic form to those of neurotic reactions to the ordinary events of life. Although they are now superseded by more recent psychiatric literature, individual passages, particularly of the *Medical Inquiries,* still are admirable for their sensitivity and perception. Of major importance is the recurring theme of the curability of mental disease which Rush was able to impress upon his students and readers and which came to supplant the long-held belief of "once insane always insane."

Rush's psychiatric writings, like those on other subjects, are impressive also because of his scholarly and scientific approach to the problems under study. In this spirit he treated the subject of "lunacy" in its literal sense. As the name indicates, mental disease had been related for centuries to the moon and the belief was prevalent that its waxing or waning induced, increased or decreased madness. Rush's observations had caused him to doubt this influence. Not being satisfied with the available literature on the subject, Rush instructed the hospital apothecary to observe the patients' reactions to the rising sun. The observer reported increased excitement at daybreak and a general tendency towards greater calm and silence at nightfall. This seemed conclusive proof to Rush for the fallacy of the lunar influence.

Rush's awareness of psychosomatic disease was far ahead of his day. In a lecture to medical students he advised them at all times to preserve a composed and hopeful outlook, for "the extent of the influence of will over the human body, has not yet been fully ascertained." While he rejected the methods of Mesmer, Rush was the first to admit his willingness "to derive . . . advantages from his deceptions . . . for the facts which [Mesmer] has established, clearly prove the influence of the imagination and will upon diseases." In availing himself of the aid which the powers of the mind present, Rush "frequently prescribed remedies of doubtful efficacy in the critical stage of acute disease, but never till I had worked up my patients into a confidence bordering on certainty of their probably good effects." In the same lecture he also exhorted his students "never to be angry at any thing a sick man says or does. . . . It is cowardice to resent an injury from a sick man; since from his weakness and dependence upon us, he is unable to contend with us on equal terms."*

In spite of these insights and the farsighted ap-

*Rush B: Medical Inquiries and Observations upon the Diseases of Mind. Philadelphia, 1812, pp 180 ff.

proaches to the treatment of mental disease, Rush could not free himself altogether from the practices of preceding days. From these he accepted the "Gyrater"—a revolving board on a pivot, on which the patient was spun around—which had been first employed in England "in chronic madness, and with great success." Another mechanical device of his own invention was a so-called "Tranquilling Chair" to calm patients in a highly excited state, since it was supposed to control the impetus of the blood towards the brain, and by lessening muscular action or reducing motor activity, to reduce the force and frequency of the pulse. None of these contrivances, however, are important enough to offset Rush's major reforms in psychiatry which changed the outlook of the mentally ill in America from one of unrelieved neglect and inevitable deterioration to one of hope of improvement and even of cure.

VIII

It is not to be wondered that Rush was often asked how he found time for all his many interests and activities. To this he answered: "I lost no time in my house. The scraps of time which interposed between the hour I returned from visiting my patients and the times of eating, I spent in light reading, or answering letters, or such pieces of business as required but little abstraction of mind. The evenings from 7, 8 or 9 o'clock when not engaged in business or company were spent in study, sometimes in the same room with my wife and children, but later in a room appropriate to my use. I seldom left it 'till 11 or 12 o'clock at night. After the year 1789 I rarely dined, or spent an evening, out of my own house."

He said that he derived rest from fatigue in reading, by writing, and from writing by reading, so as to require no other relaxation of body or mind for many hours.

Such a schedule is descriptive of the life of a bachelor rather than that of a family man. And indeed in his youth he had written to a friend: "Medicine is my wife; science is my mistress; books are my companions; my study is my grave; there I lie buried, the world forgetting by the world forgot." This monastic life ended, however, when he was 30 years of age and met the 16-year-old Julia Stockton, whose simple and intelligent praise of a Sunday sermon had won his heart. Their marriage in 1776 was followed by the births of 13 children.

Benjamin Rush's life came to an end in 1813 at the then high old age of 68. By that time, American medicine had almost caught up with that of the former mother country, England, although it was still considered desirable for a respectable physician to have spent a few years of postgraduate education in Europe. There is no doubt that the War of Independence and the very early years of American independence were medically the most difficult years of the new nation, and the consideration of Benjamin Rush, whose life bridged the years of political dependence upon England with the early years of independence, gives us profound insight into "the way it was two hundred years ago."

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Health and Disease on the Western Frontier

A Bicentennial Appreciation

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THE YEAR of our national bicentennial is a time for celebrating the many features of our history. Colonial medicine is drawing the most attention from the historians of medicine, justifiably I suppose, because it is now 200 years of age. But colonial medicine was European medicine, especially British. If one wishes to celebrate our heritage, it is the medicine of the frontier, as it moved progressively westward, that is uniquely American. As the earliest Americans believed some of their diseases and their cures to be different from those of their European homelands, so too the Western settlers believed their conditions to be peculiar to their own unique experiences. We shall see, however, that this was only partly true.

The American pioneers who moved progressively westward from the 1790's on experienced many of the same threats to their health that pioneers have always faced: new infections to which immunity had to be built up, injuries, malnutrition, poor sanitation and similar hardships. There were some conditions, however, in these predominantly 19th century migrations that were not present in previous times. The numbers and rapidity of settlement were greater and the technological developments in power, transportation, farming and building all had pronounced impact on disease conditions and medical practice, as indeed they did on all spheres of life.

What made the Western situation different was the amount of disease, its differing epidemic characteristics and the conditions under which it had to be borne. The historical epidemiology of health and disease on the frontier varied according to the factors determining the incidence and spread of any disease: time, season, climate, geographical location, crowding, sanitary conditions, and other similar physical and social factors. When speaking of disease in the West, then, one is limited in generalizations and conclusions by many things. There was no single disease, or group of diseases, that was entirely typical of the frontier or of pioneers. Some illnesses, such as malaria and scurvy, were widespread. Others, such as milksickness, were more local.

The frontiersmen, hardy as many of them were, nevertheless were subject to the usual accidents and injuries of an active life. Travel reports and diaries of the pioneers are full of accounts of major and minor accidents. Land clearing was not without its hazards. An improperly felled tree crushed more than one body or limb. The lack of surgeons and, even if surgeons did treat an injury, the lack of good antiseptic technique led to frequent amputation and to many postoperative infections. These latter could themselves be fatal at worst or very debilitating at best. And it should be said at the outset that many of the health problems afflicting the pioneers were of a distinctly debilitating nature. Illness and prolonged convalescence are difficult in the best of modern circumstances. For active frontiersmen, whose daily hard physical work was essential for survival, this often meant failure.

Certain groups of pioneers were subjected to hazards peculiar to their mode of travel or their chosen work. The miners in California, for instance, suffered innumerable injuries in open faced mining shafts, as well as from the violence rampant in some mining communities. The Indians were a constant threat, especially on the great plains and prairies. One of the earliest

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American medical journals carried a very serious article entitled, "On the management of a scalped head."

Diet in Pioneer Life

To provide sufficient daily food was a problem for most travelers and for many people already settled on the frontier. Dietary deficiency and the resistance to infections is still a topic of investigation. That severely deficient diets led to lowering the resistance, whatever that vague phrase may really mean, and to actual disease such as scurvy there is no doubt. The more subtle factors involved in diet and health are not pertinent here. The pioneers believed that many of their woes were caused by improper cooking and choice of foods. We still hear patients ascribing some of their ills to things they did or did not eat, a tradition that goes back to the Greeks.

John Woods, an English farmer who settled in the Illinois country around 1820, pointed out that although much sickness prevailed among the American settlers, the Europeans generally enjoyed good health. His explanation was that the Americans ate but two meals a day and sometimes only one, while the Europeans ate regularly three times a day. His evidence, one should hasten to add, was very skimpy, but the idea of trying to correlate eating habits of various immigrant groups to their levels of health and disease is intriguing.

Sometimes a forced change of diet led to severe intestinal disturbances. Whether a bacterial infection in our modern terms would be implicated here is not clear. But the travelers' accounts leave no doubt as to their own cause and effect reasoning: "The sudden and entire change from flesh to fish affected us all more or less, with diarrhea and pain in the abdomen. . . . " This note in the diary from the Oregon journey of John K. Townsend is typical. When the fish involved was salmon, the high fat and oil content was usually blamed for loosening the bowels. But it was not only the fatty foods that caused problems. Numerous observers of the Western scene pointed to the preparation of food as the greatest tax on the digestive powers. A military physician, writing on the causes of the prevalent diseases of the Western states in *The Maryland Medical and Surgical Journal* in 1842 charged that:

"The frying pan is the chief kitchen-implement and lard the most abundant material. Every meal, breakfast, dinner, and supper is a fry; . . . My own experience convinces me that the great influence of the prevailing diet upon the general health of the west is much over-looked, and that, a change in the culinary habits of the people, a substitution of the pot and the gridiron for the frying-pan and water for lard, would contribute more to the comfort and prosperity of the people than is at first apparent."

Thus the dietary habits were thought to lead to much ill health and to many cases of dyspepsia, called by some the typical American disease.

The Most Common Symptom

While the ague, discussed below, was the most common disease on the frontier, diarrhea must have been the most common symptom. This debilitating condition, which in the large Eastern cities killed scores of infants every summer under the name cholera infantum, occurred as often on mountain trails as on the plains. In the East the unsanitary streets and crowded tenements led to a wildfire spread of intestinal diseases, but the West had its sanitary problems as well. Everett Dick, the noted historian of pioneer life, described Lawrence, Kansas in the 1850's as "one vast hospital of sick people. Cholera, typhoid fever, the ague, pneumonia, pleurisy, small pox, and other diseases swept scores of people into eternity." In the absence of wells, which especially were lacking in the newly settled areas, water had to be obtained from springs, sloughs or waterholes, all too frequently contaminated and ready to spread their death dealing germs.

One form of diarrheal disease was the most dreaded of all—cholera, which swept through the country in epidemics in 1832, 1849 and 1866. Also known as Asiatic cholera or cholera morbus, this food-borne and waterborne bacterial disease caused great fear and panic because it was associated with the worst possible characteristics of any epidemic disease: it affected large numbers, struck extremely rapidly and caused many deaths, and the doctors really could do very little for the poor sufferers. Literature is replete with stories describing a man healthy in the morning who was in the throes of abdominal spasms with watery diarrhea leading to dehydration and prostration by evening. Soon thereafter he might be ready for burial. Even that final rite too often had to be in a ditch with dozens of his unfortunate fellow victims.

"Rain follows the plow" was a common belief on the Great Plains in the 19th century. But as

Figure 1.—Frontier physicians could spread their services more widely by circuit riding. Such hard working doctors were often away from their homes for a week or two at a time, equipped with what medicines and appliances they could carry in their saddle bags. (This photograph of Dr. Daniel Ream of Siskiyou County, California, was supplied through the courtesy of the Siskiyou County Museum, Yreka.)

rain followed the plow so did one of the most prevalent diseases the pioneers encountered—malaria, or the ague. The disease was so common that many travelers and physicians reported that often people did not even consider it as illness. "He ain't sick," the saying went, "he's just got the ager." The term malaria (literally *mal aria* or bad air) relates to its supposed origin from air filled with miasms. Since the disease reached its greatest prevalence in the fall it was also known as autumnal fever. The British term (also commonly used by Americans) was ague or fever and ague. "Chills and fever" or "the shakes" were more descriptive and popular ways of referring to this very widespread malady.

Malaria on the Frontier

Malaria is an infectious disease with intermittent symptoms, hence its common name of intermittent fever. The disease more often debilitates rather than kills its victims. In patients with repeated attacks there usually are great weakness and depression, and enlargement of the spleen in the acute phase. The economic and social consequences to those who had to do hard physical work and to protect themselves from the elements or the Indians are obvious. Those who contracted the disease while traveling were equally unfortunate.

Among doctors and laymen of the 19th century, who before very late in the century knew nothing of the parasitic cause or the mosquito spread of the disease, the miasmatic doctrine of its origin was by far the most commonly held. According to this theory the ague, and many other infectious diseases as well, was caused by decaying organic matter that poisoned the air with a noxious effluvium. Watering the land was believed to increase the formation of miasms, a belief not without foundation as we now know, because mosquito larvae breed in collections of still water.

Many observers, such as Fortescue Cuming early in the 19th century, noted that the residents along the banks of the Mississippi, where overflow with resulting stagnant water was common, had annual attacks of ague leaving the sufferers weak and sallow in complexion. While Cuming's description in 1810 is not as clear and precise in its diagnostic labels as we might want today, it nevertheless graphically portrayed the problem:

"On the subsiding of the waters, the sickly season commences, and lasts with little variation from July to October, inclusive. This is more or less the case over the whole territory, particularly on the banks of the Mississippi, and in the neighborhood of swamps and stagnant ponds. The driest seasons are the most unhealthy. The prevailing malady is a fever of the intermittent species, sometimes accompanied by ague, and sometimes not. It is rarely fatal in itself, but its consequences are dreadful, as it frequently lasts five or six months in defiance of medicine, and leaves the patient in so relaxed and debilitated a state, that he never after regains the strength he had lost. It also frequently terminates in jaundice or dropsy which sometime prove fatal.

"All newcomers are subject to what is called seasoning, after which, though they may be annually attacked by this scourge of climate, it rarely confines them longer than a few days."

Dr. John C. Gunn in his widely used home

medical adviser, *Domestic Medicine,* clearly described for his readers the course of acute malaria. There are three stages to the attack, Gunn explained, cold, hot and sweating.

"In the first there is much yawning and stretching, the feet and hands become cold, the skin looks shriveled, you seem to lose the use of your limbs by weakness, your pulse is small and frequent, you dislike to move, and finally take a chill succeeded by a cold shake. This shake continues about ten or fifteen minutes, according to the severity of the attack. In the second stage, as the chill and shaking go off, a pain in the head and back comes on, succeeded by flushings of heat and thirst, and desiring that the covering be removed that you may feel the cool air. Your face is red, your skin dry, your pulse becomes regular, hard and full. In severe attacks, where the blood determines to the head, I have frequently known delirium for a time. In the commencement of the third and last stage, the intense heat begins to subside, moisture begins to break out on the forehead gradually extending itself over the whole body, the fever abates, thirst diminishes, breathing becomes free and full, desire to make water, which deposits a sediment in the urine or pot; you then feel considerably relieved as the sweat increases, which soon restores you to your usual feelings and sensations except great weakness and extreme prostration of strength."

Obviously then, this very common malady took a terrific social, economic and physical toll, especially when one keeps in mind that the above description was of but a single attack. Depending upon which of several malarial parasites caused the infection, the patient went through these paroxysms every 24, 48 or 72 hours. The quotidian variety, with chills every 24 hours was the most common, recurrences occurring over a period of weeks if not aborted by quinine.

An Underreported Disease

Paradoxically, malaria was probably an underreported disease despite its wide prevalence. For one thing it was so common as to escape any special notice. The disease strikes small children very frequently, though in the previous century there was still current the mistaken notion that only adults were afflicted. The many clinical and lay terms applied to malaria—such as intermittent, remittent, remittent bilious, congestive, tertian, quartan and quotidian fevers—were bound to cause confusion. From the point of view of business and promotion of an area there was also reason to play down any epidemic disease. The purported report from Wisconsin that the place was so healthy that a few men had to be killed in order to start a cemetery describes this attitude very well. The truth is that throughout much of the Midwest malaria actually determined the daily habits of the people: ministers scheduled preaching to avoid their shakes and courts avoided the sick days of the litigants or the justices.

Figure 2.—An advertisement for a saddle bag designed to carry medical supplies and surgical instruments (from "The Swamp Physician," *Ohio State Medical Journal,* May 1976. Photograph by Robert Packo).

While all travelers knew that the ague, or the fever as they called it, was *the* disease of the Mississippi River Valley, it was also an important health factor in California. It was probably brought to the state by fur trappers who had become infected in an Oregon epidemic of 1829 and 1830. The disease was well established in California before the forty-niners came in such large numbers, and it continued to be present and to flare up in local epidemics through the rest of the century. The secretary of the California State

Board of Health reported in 1875 that malarial fevers and consumption were the most prevalent forms of disease.

The American experience with malaria confirms the fact that a high incidence of malaria did not immediately follow settlement of a region. Only after a few years, or even decades, did the disease present a problem. Erwin Ackerknecht, the foremost historian of malaria in the Midwest, has called this phenomenon an epidemiological latency period. One important judgment that the concept of latency period affords us is to be able to distinguish between a moving and a stationary frontier, using the evidence of sickness statistics.

Colonization of the American continent helped spread most diseases. Malaria was probably originally imported with Negro slaves, but White colonization spread it rapidly. Haphazard clearing of trees, for instance, allowing sunlight to reach previously nonexistent or shaded pools of water was important, and the early housing of the Western settlers, unbeknown to them, was ideally suited to the unwelcome but ever-present mosquitoes. Most of the malaria transmitting types of mosquitoes thrive in dark, moist, warm habitats —just the conditions provided by a log cabin. As housing improved, malaria decreased.

Malaria disappeared from the upper Mississippi River Valley before any conscious antimalarial measures such as screening were instituted. Ackerknecht cites several factors, stressing that no one reason can be singled out. The coming of railroads was important because less reliance on water transportation resulted in a shift of settlements from the bottom lands of high mosquito density to the healthier uplands. As settlements grew and prospered, livestock herds grew, and since mosquitoes much prefer cows to men the chances for malaria passage were reduced.

Typhoid Fever Increases

There is evidence that around the middle of the last century typhoid fever gradually replaced malaria as the prevalent disease of the Midwest. Typhoid is a severe intestinal disease caused by a bacterium that is readily spread by flies, food, fingers and water. It was an ever-present threat wherever sanitation was lax, that is to say in most communities and settlements. Until proper sewage disposal was instituted and clean water made available, diarrheal complaints were routine. Some of these doubtless were due to typhoid, or continued fever as it was often called. Not until 1836 did Dr. William Gerhard, a Paris trained physician of Philadelphia, clearly differentiate between the louse-borne disease typhus fever, also called ship fever or jail fever, and typhoid fever. The latter disease could be found in the gold rush mining camps, along the trail, as well as in the large cities of the East or the new towns of the frontier.

Scurvy, ever the bane of travelers, was no less a problem in the great migration to the American West. Now known to be caused by vitamin C deficiency, the disease comes on slowly when the diet is deficient in natural sources of the vitamin, especially fresh fruits and vegetables. During much of the migratory period travel was slow and food preservation not yet sufficiently advanced. Among the forty-niners the disease was especially prone to appear when they first tried to do hard physical work upon reaching the mines after the long water or overland journey.

Scurvy was often confused with rheumatism because muscle weakness and pain were common symptoms. Late manifestations, appearing after 150 to 200 days of vitamin deficiency, included skin lesions, swollen gums, swelling of the limbs and anemia. The disease, as is apparent from the list of signs and symptoms, causes severe lethargy, in itself very serious. The emigrants usually made some provisions against scurvy on the trip west, but too often these were insufficient. The settlers knew which roots or fruits were good antiscorbutics. Service berries or June berries, for instance, were abundant in some areas. These we now know are rich sources of vitamin C.

One apparently common health problem of women, rarely discussed in the travel journals and diaries, was prolapse of the uterus. Dr. William M. Wood of the United States Navy, previously quoted on the evils of the frying pan, told his colleagues that this condition ". . . among the women of the new states, presents itself to an extent so shocking as to indicate some sectional causes. So numerous are the cases that a pessary, with those who use it, is almost as essential an appendage of a doctor's saddle bags as a pill box." Wood ascribed the frequency of uterine prolapse to the conduct of labor in childbirth and the subsequent medical management of the new mother. "It is a matter of religious vigilance," the outraged Dr. Wood continued, "during the progress of labor, to harass the patient by all manner of savage and violent aid . . . and by no manner or means permitting her to remain quiet in bed."

Where no physicians were available, as in isolated settlements or in the backwoods or on the trail, Wood blamed the barbarous practices on "old women" who managed the labor process. This harsh judgment should certainly not be applied to all the many midwives who did much creditable obstetric work throughout the frontier country.

As to psychological problems, the types and extent of these disorders among the pioneers are difficult to describe and to measure. The active habits of our countrymen, one observer wrote, made hypochondria much rarer than in Great Britain. One recent writer has drawn attention to the unimaginable solitude of the early West. The extent of its havoc is glimpsed in a few diaries, but the real toll is yet to be measured with any real precision.

One of the diseases encountered by the pioneers was truly a frontier disorder, the awesome and bewildering milksickness. Often called milksick, or by even more descriptive names such as puking fever, swamp sickness, the tires, the slows or the trembles, this affliction of man and cattle was widely prevalent in the states of the upper South and the Midwest. Reports from colonial times to the 1960's may be found in the medical literature, and many family tragedies resulted from this poorly understood disease.

The Cause of Milksickness

We now know that milksickness is due to poisoning with tremetol, the toxic ingredient of white snakeroot and rayless goldenrod. The disease occurs after cows eat the leaves or stems of the white snakeroot plant and when man then eats butter or drinks milk from the poisoned animals. Exact figures are not obtainable, but the incidence of disease and death from this cause in 18th century and 19th century America was great. It was especially prevalent in dry seasons when cattle strayed from their pastures into neighboring woods. In newly cleared areas without fenced pasturelands the disease was more likely to occur than in more settled regions with fences. Another important epidemologic point is that the toxin in raw milk must reach fairly high concentrations to do its damage to human consumers. In rural areas where heavy consumption of raw milk from single cows or a small herd was common, the disease was likely to hit entire families. In more populous areas, where milk from several sources was pooled, the toxin was diluted, hence less harmful.

The disease is directly related to the dose of toxin absorbed. Severe acid-base disturbances could lead to death within a few days. Such was the plight of the community of Pigeon Creek in Indiana when Nancy Hanks Lincoln died of milksickness in 1818 when her son Abraham was a boy of 9. Mrs. Lincoln's great aunt and uncle and two neighbors died shortly after her. Though Nancy Hanks Lincoln may have been the most prominent historical figure to die of milksickness on the frontier, she was by no means the only one. Those lucky enough to recover after an illness characterized by loss of appetite, weakness, muscle pain and stiffness, severe vomiting and constipation, were often left to a slow recovery with much lethargy. This feature gave it the name sloes or slows.

Finally it should be said again that other diseases such as diphtheria, smallpox, tuberculosis, erysipelas and various skin disorders, were as prevalent in the West as they were in the East. In fact, a significant number of emigrants came west in search of health. The lands beyond the Missouri were supposed to be rich as well as invigorating. An outdoor existence in the mountains of Colorado certainly proved beneficial for some consumptives, but they soon encountered numerous other threats to their health. While preservation of good health was but one of many problems faced by the pioneers, it was an overriding one. Without health all else might be lost. And, unfortunately, in most instances, 19th century Americans had little direct control over disease and its prevention.

Much of the treatment of disease was left to family members who relied on innate wisdom and the help of a variety of do-it-yourself home medical advisers. As Mark Twain recalled it in his autobiography, "Doctors were not called in cases of ordinary illness; the family grandmother attended to those." The frontier doctor, at any rate, rarely could rely on the income from his practice to make ends meet. Only after establishing himself solidly and only after his patients themselves had become economically self-sufficient, could the doctor expect to make a decent living from medicine.

A Variety of Doctors

Many men practiced many different brands of medicine or followed various doctrines regarding diseases and cures. That many practiced who were not properly educated to the profession was

true throughout the country. Licensing laws were repealed in most states by the middle of the 19th century. Pretty much anyone who called himself doctor could function as one. In the new settlements many men held life and limb in their hands with little more than good intention to go on. Sometimes the title of doctor was thrust upon those who, by virtue of good common sense and a bit more education than their fellows, sounded and looked like doctors. The experience of one pious New Englander, Estwick Evans (who was born in 1787) must have been very common. While traveling on the Ohio River, he wrote, the boatmen, who frequently became sick with fevers, applied to him for medical aid: " . . . and hence I acquired the title of Doctor. My prescriptions were always simple; and, strange to tell, I did not lose a single patient. . . . I always told the sick, that in a few days, they would be perfectly well." Evans was a firm believer in nature's power to cure. In this he was in the best company, for by midcentury a movement toward a less heroic form of treating, without bleeding, purging and blistering, was well under way.

Where doctors were unavailable their writings were not. The home medical adviser, usually a book written for the public in nontechnical language by a physician, was among the standard equipment of most pioneer wagons or pack trains. These guides began to be published with increasing frequency from the 17th century on. John Wesley was as widely known for his *Primitive Physick* as he was for his particular brand of Christianity.

The titles of some of those do-it-yourself medical books plainly indicate their intentions. An early 19th century example was Alexander Thomson's *The Family Physician; or, Domestic Medical Friend: Containing Plain and Practical Instructions for the Prevention and Cure of Diseases.* Another was *House Surgeon and Physician; Designed to Assist Heads of Families, Travellers, and Sea Faring People.* An English book of the late 18th century that went through numerous editions and dozens of reprintings in this country was William Buchan's *Domestic Medicine.* The later editions even included sections dealing with the care of livestock.

Which of these many domestic medical guides was the best or the most popular is hard to gauge. Certainly a prominent candidate would have to be Gunn's *Domestic Medicine, or Poor Man's Friend,* written by Dr. John C. Gunn of Virginia and Tennessee in 1830. A conservative estimate is that the early editions in the 1830's sold over 100,000 copies. By the 1860's it was much enlarged and still going strong, a best seller by any standard.

Dr. Gunn was convinced that medical knowledge need not be esoteric, that the time had come when all the technical language of medicine should be made plain to the people. He aimed his book at the unlearned. They needed instruction to help them live healthier lives and to avoid the many schemes and medicines of the quacks that abounded. Gunn's rules for health were simple: exercise, temperance and cleanliness.

How the pioneer physician actually practiced his profession and what modes of therapy he prescribed depended on his training, on his allegiance to the so-called regular profession or to one of the numerous medical sects, and on the availability of medical supplies. Some generalizations can be made. Since fevers were very common, some form of depletion therapy was usually used. Bloodletting was especially popular until the Civil War years. Several ounces to a pint or two might be let at one time by cutting into a vein or scarifying the skin. Leeches did the job more slowly. The theory was that a vascular fullness existed at the onset of an illness. This had to be reduced before any drug therapy could be effective.

Therapy Based on Humoral Theory

In a similar way emetics and strong purges were used. All this therapy was based on the age-old humoral theory of disease. Blood, yellow bile, black bile and phlegm were the four humors of Greek antiquity. These combined in hot, cold, moist and dry combinations. If the humors were unbalanced or in the wrong location within the body they might be favorably affected by release through the intestinal tract or via the blood vessels. By a theory of opposites, treatment was directed to cool those diseases deemed to be hot, dry those with excess moisture and the reverse.

The most commonly used purge was mercurous chloride, better known as calomel. Nineteenth century doctors believed that in addition to acting as a cathartic, calomel modified the secretion of the liver. That organ was believed to be sluggish in most fevers and in spring time.

To illustrate therapeutic concepts and their vagueness, witness what a physician writing on the "Modus Operandi of Calomel" in the *Western*

Journal of Medical and Physical Sciences in 1833 had to say: "When given in large doses, besides its primary action on the bowels, it produces its specific effects on the general system, called the mercurial impression: and this, whatever may be its nature, seems more especially to affect the capillary vessels, and the receiving and absorbing systems. By exerting the action of these parts, it has a tendency to equalize the general circulation, restore secretions, overcome local congestion, inflammations, etc."

We now know that there was some justification for thinking that calomel acts on a sluggish liver. Calomel causes a greenish stool, *not* because it stimulates an increased bile flow from the liver, but because mercury, acting as a mild antiseptic, interferes with the intestinal bacteria that are necessary to convert the stools to their normal color by acting on the bile pigments being excreted. Calomel also causes salivation, and when given for too long a period or in excess causes bone damage and teeth to loosen and actually drop out. The salivation was thought to assist in ridding the body of bad humors.

A typical picture of an early 19th century American practitioner is one drawn by J. Fenimore Cooper. In his novel *The Pioneers,* Cooper portrayed frontier life in the 1790's. As such it is one of the first and most useful novels for our purpose. One of Cooper's characters is the young physician of formidable stature, Dr. Elnathan Todd. Elnathan, a sickly lad, took to doctoring because it was believed to be an easier calling than farming. After an apprenticeship with a local doctor and a very brief sojourn in the hospital at Boston, the young man was ready to minister to the ills of an upstate New York frontier village. Elnathan, Cooper tells us, " . . . had acquired a certain degree of knowledge in fevers and agues, and could talk with much judgement concerning intermittents, remittents, tertians, quotidians, etc. In certain cutaneous disorders very prevalent in new settlements he was considered to be infallible. . . . " Dr. Todd's surgical skills were perhaps questionable, but then what newly independent physician's were not?

As Cooper noted, Dr. Todd's " . . . reputation was hourly increasing, and, luckily for his patients, his information also." The descriptions of his ministrations to the victims of a gunshot wound vividly pictured a scene that must have been reenacted countless times in the 100 years to follow. Dr. Todd carefully emptied the contents of his saddle bags and surgical case in preparation for dressing the wound. There were various phials filled with radiant colored fluids arranged on the table by the side of "murderous" saws, knives and scissors, all with due effect on the audience. The doctor then successfully extracted a large shot from his patient's leg.

This scene and the actors in it were typical of 19th century frontier medicine. Dr. Todd's training, or lack of it, and his empirical skills also exemplify most doctors of a century ago. Many areas in the West suffered from a lack of physicians, qualified or unqualified. From the 1830's on, some Western medical schools were founded in order to increase the number of available doctors. Along with numerous other reports, that of S. H. Long's expedition to Arkansas related that "Among recent settlers, the want of the most common comforts, of the advice and attendance of skillfull physicians, and, above all, the want of cleanliness, and the destructive habits of intemperance, are causes operating powerfully to produce and aggravate . . . diseases."

Medical Circuit Riders

One means by which doctors could spread their services more widely was by circuit riding (Figure 1). Lawyers and preachers also carried out their duties in this fashion. The hard working medical circuit riders were away from their homes for a week or two at a time, living with their patients en route. Gathering herbs along the trail and equipped with what medicines and appliances they could carry in saddle bags (Figure 2), these were among the earliest pioneer doctors in the West. When roads improved and railroads were built consultation became easier. With the advent of the telephone, circuit riding was no longer necessary.

Much research still needs to be done to determine with any degree of accuracy how many physicians practiced at any given time in urban as well as in rural areas. Just what an average patient could expect in his encounter with a physician has not been fully elucidated by any means either. In honoring the work of these early Western physicians, it seems fitting to recall not the exploits of the few who achieved fame, such as Ephraim McDowell, William Beaumont and Daniel Drake, but the countless numbers who bore the harsh burdens of pioneer life along with their fellow Americans. While there was toil and turmoil aplenty, optimism and a sense of the future was every bit as prevalent.

Specialty Conference

Moderator
PHYLLIS A. OILL, MD

Discussants
THOMAS T. YOSHIKAWA, MD
TERRY YAMAUCHI, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Refer to: Oill PA, Yoshikawa TT, Yamauchi T: Infectious disease emergencies—Part I: Patients presenting with an altered state of consciousness, *In* Infectious disease emergencies—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conference). West J Med 125:36-46, Jul 1976

Infectious Disease Emergencies

PART I:

Patients Presenting with an Altered State of Consciousness

PHYLLIS OILL, MD:* This is the first part of a five part symposium concerned with medical emergencies related to infectious diseases. The format of this symposium is based on the major symptom complex that a patient may exhibit when presenting to an emergency department or physician's office. At the beginning of each section of the symposium there is a chart of the various infectious diseases that may be etiologically responsible for the patient's clinical symptomatology (see Table I-1). Only those entities most commonly associated with the clinical situation being considered in the particular part of the symposium will be discussed. The other listed infectious processes will be covered in those sections in which the clinical factors related to that disease entity are most dominant. For example, although infective endocarditis may manifest in a patient as an altered state of consciousness it will be discussed in the section dealing with patients who present with cardiac decompensation (Part II).

The first part of the symposium will consider those infectious diseases that may primarily cause an altered state of consciousness in a patient. Patients presenting to the emergency department with alterations of their sensorium (such as lethargy, stupor or coma) pose a difficult diagnostic and therapeutic problem to a physician. The urgency and complexity of this clinical state are due to several factors:

- Rapid irreversible brain damage may occur unless decisive therapeutic interventions are quickly employed;
- Key and important medical history is often unobtainable;
- The differential diagnoses are numerous, and
- Rapid mobilization and assistance from various medical and surgical specialties (such as neurologist, neurosurgeon, neuroradiologist, cardiologist and infectious disease specialist) may be necessary in the total management of the patient.

It is beyond the scope of this symposium to systematically discuss all the possible causes of lethargy, stupor and coma, or how to differentiate each clinical entity. However, a list of the more common disease states that may present as alterations of the sensorium is shown in Table I-2. The list is by no means complete but it should provide physicians with a practical differential diagnosis when faced with a patient with this clinical problem.

The first discussant is Dr. Thomas Yoshikawa, who will address himself to the topic of suppura-

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Part 1 of a five part symposium. Parts II through V will be published in subsequent issues.

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
HSV = herpes simplex virus
KOH = potassium hydroxide
LP = lumbar puncture
PMN = polymorphonuclear

tive intracranial processes: meningitis, brain abscess, subdural empyema and cerebral phycomycosis. Dr. Terry Yamauchi will then discuss viral meningitis and encephalitis. In addition, he will consider Reye's syndrome, which often follows a viral-like illness although an etiologic agent has yet to be determined.

THOMAS T. YOSHIKAWA, MD:* In keeping with the purpose of this symposium, the discussion will be directed toward diagnosis and management of intracranial infections that may present in the patient as lethargy, stupor or coma. Helpful clues which may assist the physician in suspecting an intracranial infectious process are listed in Table I-3. Although none of these findings will specifically rule in or rule out an intracranial infection, they may heighten the suspicion of the physician toward this diagnosis. Failure to make a rapid diagnosis and begin appropriate therapy is the major reason for the morbidity and mortality seen in patients with intracranial infections.

Meningitis

Meningitis, especially those types with bacterial causes, epitomizes the major impact antimicrobial agents have made in the modern practice of medicine. Before the antimicrobial era, bacterial meningitis was a disease with a *mortality* exceeding 90 percent. However, with early diagnosis and institution of appropriate antimicrobial therapy, the *cure* rate can approach 90 percent. Therefore, it is imperative that the physician—whether it be in an emergency room, clinic or office—who first sees a patient exhibiting lethargy, stupor, coma or even more subtle central nervous system (CNS) signs be keenly attuned to this possible diagnosis.

Clinical Features

Some of the helpful clinical findings in suspecting meningitis are listed in Table I-3. The usual rapidity in which the symptoms and signs appear in patients with meningitis, in association with fever, makes it absolutely essential that physicians think *first* of meningitis—until it can be proved not to be present. However, in nonbacterial meningitis (tuberculous or fungal) the clinical features may be more gradual and indolent. More subtle clinical findings may be the predominant feature, such as a change in personality, mild confusion and low-grade fever. A history of tuberculosis, abnormal findings on an x-ray film of the chest, appropriate travel history, underlying malignancies or use of immunosuppressive drugs may be helpful clues to direct physicians in considering meningitis in these less overt presentations.

Diagnosis

Once the possibility of meningitis is suspected, examination of the cerebrospinal fluid (CSF) is the *sine qua non* in confirming this diagnosis. A lumbar puncture (LP) should then be carried out. However, before an LP is done, the physician should consider whether a *localized* intracranial suppurative process (for example, brain abscess or subdural empyema) may be a strong consideration in the differential diagnosis. (The clinical features of these two disease entities will be subsequently discussed.) If this is the case, a brain scan or arteriogram, or both, should be done *before* initiating a lumbar puncture to confirm or exclude these possibilities. Whereas a lumbar puncture is essential for the diagnosis of meningitis, it is potentially hazardous in the presence of a localized intracranial suppurative (or mass) process.[1] Because of the significant risks of herniation syndromes, the hazards of an LP with the latter disease entities far outweigh the useful information that can be obtained from examination of the CSF. In situations where meningitis is associated with intracranial hypertension, or both a meningeal inflammatory process and localized intracranial suppuration (for instance, brain abscess rupturing into the subarachnoid space) are operative, a cisterna magna puncture would be an alternative diagnostic approach for obtaining CSF.

Once a lumbar puncture is carried out, CSF manometric, protein and glucose determinations; cell count with differential; appropriate cultures, and Gram stain should be done. A useful approach in assisting physicians in suspecting a bacterial versus nonbacterial meningitis is to sep-

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arate the CSF white cell count into predominately polymorphonuclear (PMN) response or predominately lymphocytic response. Listed in Table I-4 are the various diagnostic possibilities of an abnormal CSF pleocytosis. A preponderance of PMN's (arbitrarily defined here as 90 percent or greater) is most often associated with untreated bacterial meningitis. However, early in viral (aseptic), tuberculous or fungal meningitis it is possible to see a major PMN response in the CSF. The clinical course, rapid reversion of the CSF to primarily lymphocytes, absence of bacteria on smear or culture and relatively normal spinal fluid glucose levels will strongly suggest a viral cause. The numerous causes of CSF lymphocytosis make it imperative that physicians systematically approach the various diagnostic possibilities, keeping foremost in mind those CNS diseases that are treatable (for instance, tuberculosis, fungal infection, brain abscess, subdural empyema).

The importance of a Gram stain in every case of suspected meningitis cannot be overemphasized. A Gram stain will give positive results 75 percent of the time in patients with culture-proven bacterial meningitis.[2] It is inexpensive, simple, rapid and oftentimes diagnostic. However, the absence of visible bacteria on smear does not exclude the possibility of bacterial meningitis and, therefore, results of the CSF culture become very important. Although the yield may be low, acid-fast smear and India ink preparation should be routinely carried out on CSF.

Cerebrospinal fluid cultures for bacteria, fungi, mycobacteria and virus should be obtained in all patients suspected of having meningitis. The most common bacterial causes of meningitis are pneumococci, Hemophilus influenzae and meningococci.[2-4] Because the latter organism is fastidious, it is important to emphasize that the CSF should be directly inoculated onto a chocolate agar plate at the *bedside*. Additionally, the yield in recovery of meningococci on chocolate agar may be increased if the plate is warmed at least to 25°C before inoculation, since the organism grows best at 35 to 37°C.[5] It should be remembered that if patients have received antibiotics previously, the CSF culture may be negative despite the clinical features and other CSF measurements suggesting a bacterial meningitis.[6,7]

The CSF glucose level is most often depressed (hypoglycorrhachia) in bacterial causes of meningitis but less so with viral causes. Exceptions to this are mumps meningoencephalitis[8] and occasionally herpes meningitis.[9] In tuberculous and fungal meningitis there can also be low values for CSF glucose.[10,11] Normally, the glucose in the CSF will be approximately 60 percent of the blood glucose value;[12] values less than this are usually abnormal.

The spinal fluid protein level is generally elevated to a greater degree in bacterial (and tuberculous or fungal) meningitis compared with that in viral meningitis. However, because of the tremendous overlap that often occurs, this measurement has limited value in assessing possible causes of meningitis.

Other diagnostic studies that are extremely helpful are blood cultures and fungal serology. The former yields positive findings in at least 50 percent of patients with bacterial meningitis.[2] The latter test, in addition to fungal culture, is most useful in diagnosing coccidioidal and cryptococcal meningitis. With coccidioidal CNS involvement, any titer in the CSF complement fixation test is significant.[13] Furthermore, a rising complement fixation titer in the serum, especially

TABLE I-1.—*Infectious Diseases Presenting as Altered States of Consciousness*

- Intracranial infections
  - Meningitis
  - Subdural empyema
  - Brain abscess
  - Cerebral phycomycosis (mucormycosis)
  - Encephalitis
  - Viral meningoencephalitis
- Reye's syndrome
- Infective endocarditis*
- Septic shock*
- Retropharyngeal abscess with CNS extension†
- Necrotizing pneumonia with respiratory insufficiency†

*Discussed in Infectious Disease Emergencies, Part II: Patients Presenting with Cardiac Decompensation and Circulatory Insufficiency (Shock).

†Discussed in Infectious Disease Emergencies, Part III: Patients Presenting with Respiratory Distress Syndromes.

TABLE I-2.—*Differential Diagnosis of Lethargy, Stupor and Coma*

- Cranial trauma
- Cardiovascular
  - Hypoperfusion (sepsis, cardiogenic, hypovolemic, etc.)
  - Cerebrovascular (bleed, thrombosis, emboli)
- Metabolic (hypoxemia, electrolyte imbalance, hypoglycemia, hyperglycemia, acidosis, uremia, hepatic failure, hypothyroidism, etc.)
- Drugs and toxins (heroin, sedative-hypnotics, alcohol, bromides, arsenic, etc.)
- Noninfectious intracranial mass lesions (primary tumor, metastatic lesions)
- Intracranial infections (brain abscess, subdural empyema, meningitis, encephalitis, phycomycosis)

above 1 to 32, suggests disseminated disease. Cryptococcal serology is best utilized by measuring for cryptococcal antigen and antibody,[14,15] both in the CSF and serum.

Treatment

Therapy of bacterial meningitis is fairly straightforward based on knowledge of the most common pathogens isolated in this disease. In the adult population, pneumococci and meningococci are the most common CSF isolates. Penicillin G given intravenously in large doses (20 million units per day) is the drug of choice for these two organisms. Ampicillin may also be used with almost equal efficacy. If patients are allergic to penicillin, chloramphenicol (4 grams per day) given intravenously is the alternative agent of choice. The cephalosporins should be avoided because of their relative ineffectiveness in the treatment of bacterial meningitis.[16] In an immunosuppressed person or patients with malignancy, unusual pathogens such as Listeria or Gram-negative bacilli are more commonly isolated.[17] In the absence of a definitive identification of an organism, the initial choice of antimicrobial therapy in these patients with presumed bacterial meningitis will have to be effective against these pathogens. With Gram-negative bacillary meningitis, parenteral gentamicin alone may not suffice and intrathecal supplementation often is necessary.[18] An accepted regimen would be gentamicin given intravenously at a dose of 5 mg per kg of body weight per day with intrathecal gentamicin administered every 18 to 24 hours in a dosage of 4 to 8 mg.[19]

In the pediatric age group, H. influenzae, meningococci and pneumonococci are the major bacteria recovered from the CSF. Therefore, ampicillin given initially, until specific identification of the organism can be made, is the drug of choice. The recommended dosage for ampicillin is 200 to 300 mg per kg of body weight per day. Chloramphenicol can be substituted in penicillin-allergic patients. Also, in areas where there is a high incidence of ampicillin-resistant H. influenzae, both ampicillin and chloramphenicol may be instituted until sensitivity data return. Then one or the other antibiotic can be discontinued, based on this information. In neonatal bacterial meningitis, Gram-negative bacillary organisms are frequently isolated and, therefore, appropriate therapy for these pathogens must be provided.[20]

With partially-treated meningitis (patients receiving prior antibiotics), appropriate cultures still should be obtained. Initiation of antibiotic therapy will be a clinical judgment depending on toxicity of the patient, clinical history and abnormalities found in the various CSF measurements. If antimicrobial agents are withheld, it is imperative that the patient be carefully observed and the CSF reexamined in 12 to 24 hours. Delayed response or unexpected deterioration should prompt the physician to begin antibiotic therapy. Either penicillin G or ampicillin would be the agent of choice.

Tuberculous meningitis should be treated with a minimum of two drugs, preferably isoniazid and

TABLE I-3.—*Clinical Findings Helpful in Suspecting Intracranial Infections*

Exclude other causes by history, physical examination and laboratory data
History or presence of:
- upper and/or lower respiratory infection;
- pericranial infection (ear, mastoid, sinuses);
- penetrating head injuries, craniotomy;
- fever, nuchal rigidity, focal neurological signs;
- evidence of peripheral infections—i.e. endocarditis, lung abscess, empyema;
- heart disease with right-to-left shunt

Abnormal lumbar puncture
Avoid lumbar puncture in suspected brain abscess or subdural empyema
Think of diagnosis

TABLE I-4.—*Differential Diagnosis of Cerebrospinal Fluid Pleocytosis*

Predominantly Polymorphonuclear cells (PMN) (>90 percent)
- Bacterial meningitis
- Early viral meningitis
- Early tuberculous or fungal meningitis
- Occasionally brain abscess or subdural empyema
- Chemical arachnoiditis

Predominantly Lymphocytes (<90 percent PMN's)
- Viral meningitis or encephalitis (ECHO, Coxsackie, mumps, herpes)
- Tuberculous or fungal meningitis
- Partially-treated bacterial meningitis
- Central nervous system syphilis
- Brain abscess or subdural empyema
- Leptospirosis
- Listeria (variable)
- Cysticercosis (Taenia solium)
- Naegleria meningoencephalitis (variable)
- Central nervous system collagen vascular disease
- Central nervous system tumor
- Cerebrovascular accident
- Subdural hematoma
- Multiple sclerosis
- Central nervous system sarcoidosis
- Guillain-Barré
- Etc.

ethambutol. Whether addition of a third agent such as streptomycin is advantageous is unclear. With proven tuberculous meningitis, use of corticosteroids may have some value, especially in the face of cerebral edema or spinal block.[10] In patients with suspected but not documented tuberculous meningitis, use of corticosteroids should be avoided since the possibility of fungal meningitis must still be excluded. Steroids may enhance disseminated fungal disease.

Fungal meningitis can only be effectively treated with parenteral amphotericin B. Coccidioidal meningitis requires not only intravenous but also intrathecal administration of amphotericin B. Therapy is prolonged, often requiring up to a total of 5 grams of this drug for clinical and bacteriologic cures. Cryptococcal meningitis may not require intrathecal administration of amphotericin B, depending on severity of the disease and clinical status of the patient. The role of 5-fluorocytosine in the treatment of fungal infections has yet to be clearly defined, although preliminary data appear somewhat promising.[21,22]

The usual viral (aseptic) meningitis is caused by the enteroviruses, mainly Coxsackie and ECHO. Treatment is mainly supportive since the disease is usually self-limited. Dr. Yamauchi will further elaborate on this topic.

Brain Abscess

The topic of brain abscess has been recently reviewed in a symposium published previously in the WESTERN JOURNAL.[1] For a detailed discussion of this disease entity, the reader should refer to that article. However, a few major points are worth reemphasizing.

Although antibiotics have made a major impact on the mortality of most infections including bacterial meningitis, the death rate in cases of brain abscess has not improved in the past 20 years. A mortality rate of approximately 40 percent has been fairly constant. Those reports of higher survival rates most likely reflect earlier diagnosis and therapy.[23]

Earlier diagnosis depends on increased clinical suspicion by physicians. Although brain abscess is an infectious process, its clinical presentation may not be one of a classical infection (fever, chills, leukocytosis and so forth). Rather its initial mode of presentation may mimic other noninfectious intracranial processes.

A useful approach to classifying the types of clinical presentation in cases of brain abscess has been recently discussed.[1] Briefly, this approach categorizes brain abscess into four basic clinical syndromes, which are listed below.

- Type I—*Rapid Focal Mass Expansion*

Patients appear with symptoms and signs of a rapidly progressive, localized intracranial mass lesion. Neurological progression may be rapid, usually in days to weeks but occasionally within hours. The initial differential diagnosis often includes spontaneous intracerebral hematomas, metastatic neoplastic tumors and malignant astrocytomas.

- Type II—*Intracranial Hypertension*

With this syndrome, the clinical presentation is one of predominantly neurological deterioration secondary to intracranial hypertension. Complaints of nausea, vomiting, headache and alteration of mental function and personality are commonly seen. Papilledema is a common finding. Focal neurological deficits may also be present but are not the major component of this syndrome.

- Type III—*Diffuse Destruction*

Signs and symptoms of a rapid progressive, destructive brain process characterize' this syndrome. In these patients there is neurological deterioration out of proportion to estimated intracranial pressure. Papilledema is generally not present with deterioration occurring in the absence of brain herniation. Usually patients with multiple cerebral emboli present in this manner.

- Type IV—*Focal Neurologic Deficit*

Clinical features of focal neurologic deficits evolving slowly is the major finding in this type of brain abscess presentation. A meningioma or slowly growing, benign glioma is often the initial diagnosis.

Knowledge of the various predisposing factors for the development of brain abscess will often assist in heightening the suspicion for this infection. *Pericranial infection* (ear, mastoid or sinus) is a common source of infection preceding the development of brain abscess. *Hematogenous* or *metastatic* spread of infection from a distant focus is not uncommonly encountered as a cause of abscesses of the brain. Pulmonary infections (such as empyema, abscess or bronchiectasis), peripheral osteomyelitis, intraabdominal infec-

tions and infective endocarditis are frequent sources. Brain abscesses secondary to endocarditis tend to be multiple and are associated with high mortality. *Congenital heart disease* with right-to-left shunt is also a frequent predisposing factor to brain abscess. The associated cerebral intravascular thrombosis and right-to-left shunt, allowing bacteremia to bypass the lung, are probable important pathogenic mechanisms. *Cranial trauma* or *surgical operation* may lead to brain abscess formation either by direct implantation of microorganisms into cerebral tissue or by extension of secondary infected scalp, bone flap or cranial osteomyelitis.

The microbial flora of brain abscess is predominantly aerobic and anaerobic streptococci and coagulase-positive staphylococci. Aerobic Gram-negative bacilli are also encountered but with a lesser incidence. Mixed infections of several organisms including anaerobes and aerobes are not uncommon.[23] Familiarity with the microbial flora of the various infected predisposing sites, which result in subsequent development of brain abscess, will often assist in anticipating the types of pathogens that may be encountered with this infection. For example, pericranial infections are often caused by anaerobic and aerobic streptococci; cranial injuries are commonly secondarily infected with coagulase-positive staphylococci and occasionally aerobic Gram-negative bacilli. Additionally, patients' underlying disease may play a significant role in kinds of pathogens isolated in brain abscess—for example, in cancer patients almost half of the organisms recovered from cerebral abscesses are Gram-negative bacilli.[17]

Therapy of brain abscess is two-fold: institution of antimicrobial agents with concurrent surgical evacuation of the abscess. Use of antibiotics alone will not suffice. This was adequately shown in a recent report of six cases of brain abscess which failed to respond to antibiotic therapy alone, despite therapeutic concentrations of the agents in the abscess fluid.[24] Also implied in this study was that initiating antimicrobial therapy did not alter the yield of bacteriological data. If proper culture techniques including anaerobic methods are used, isolation of pathogens in a significant number of instances should be anticipated.

The choice of initial antibiotic therapy should be determined on the basis of the Gram stain results on the abscess fluid. By and large this therapy will generally be use of penicillin since most of the pathogens isolated from brain abscess reported in the literature are sensitive to this agent. However, if staphylococci, Gram-negative bacilli or Bacteroides are seen on smear, appropriate antimicrobial agents for these organisms should be selected. Ultimate chemotherapeutic management will rest on culture identification of the pathogens.

Once the diagnosis of brain abscess is strongly considered, surgical evacuation must be contemplated. If any delay in a drainage procedure is anticipated, intravenous administration of penicillin G, 20 million units a day in divided doses, should be instituted before surgical operation. In penicillin-allergic patients, chloramphenicol, 4 to 6 grams a day given intravenously, would be an alternate choice. Initiation of antimicrobial therapy as soon as possible is important because (1) the associated cerebritis can only be effectively managed with chemotherapeutic agents and (2) prevention of potential bacteremia and contamination of surrounding cerebral tissue during operation may be minimized. From the previous study mentioned,[24] it would not be anticipated that the yield of cultural data should diminish with institution of immediate antibiotic therapy. Systemic antibiotic therapy should be maintained for at least 2 to 3 weeks after surgical drainage. Longer duration of treatment may be necessary depending on the extent of disease and clinical response.

The choice of surgical drainage technique is beyond the scope of this symposium, and details of this can be found elsewhere.[1] However, it should be emphasized that *early surgical intervention* and *adequate drainage* are key factors in the patients' ultimate prognosis.

Subdural Empyema

Subdural empyema is another central nervous system infection classified under localized intracranial suppurative process. It is often discussed together with brain abscess because of the similarity in clinical presentation, microbiological flora and therapeutic management. Therefore, a lengthy discussion will not be presented on this clinical entity.

A few salient features of this disease, however, should be emphasized. The infection is a collection of purulent material in the subdural space and is essentially an abscess. The most common predisposing factor to the development of subdural empyema is an associated sinusitis, most

commonly frontal sinus involvement. In a patient presenting with rapidly developing, focal neurological symptoms and signs with an associated sinus infection, this diagnosis should strongly be considered. Often such patients initially may be thought to have bacterial meningitis. However, helpful clues in differentiating these two entities are (1) the presence of focal neurological signs in subdural empyema which is less common in adults with bacterial meningitis (unless the patient is severely ill); (2) the cerebrospinal fluid in subdural empyema may be "benign" (there may be only mild changes in cells, protein and glucose) as compared with that in bacterial meningitis.

The microbial flora of subdural empyema has been recently reviewed.[25] Streptococci and staphylococci have been most frequently isolated in the past. However, with more sophisticated anaerobic techniques, the role of anaerobic bacteria in subdural empyema appears to be increasingly important. Again, as in brain abscess, the so-called "sterile" subdural empyema may be related to the failure to adequately isolate anaerobes.

The management of subdural empyema is similar to that of brain abscess. Use of antibiotics in concert with surgical drainage are the key elements for a successful therapeutic outcome. The approach to antimicrobial therapy should be the same as in patients with brain abscess. Moreover, because of the similarity in microbial flora in both subdural empyema and cerebral abscess, the choice of antibiotics will not be dissimilar.

Cerebral Phycomycosis

Cerebral phycomycosis is caused by aerobic, saprophytic fungi belonging to the class Phycomycetes. The three species of organisms in this class most commonly associated with disease in man are the genera Mucor, Rhizopus and Absidia.[26] The organisms appear as broad, nonseptated branching hyphae which are ubiquitous in decaying vegetation, fruits, soil and manure. They may be found normally in human orifices (nose, throat and rectum) and are generally noninvasive. However, under certain disease conditions the organism can become highly virulent with invasion into blood vessel walls and subsequent thrombosis and tissue necrosis.[27] Diabetes mellitus with ketoacidosis is most frequently associated with cerebral (rhinocerebral) phycomycosis. Additionally, other predisposing factors include burns, uremia, diarrheal diseases, immunosuppressive states, prior antibiotic therapy and blood dyscrasias. Besides eye and central nervous system involvement, phycomycosis has been reported to occur in other sites such as maxilla,[27] ear[28] and lung,[29] or may disseminate to any organ or tissue in the body.[27]

The pathogenesis in cerebral phycomycosis is initially the development of local lesions in the oral cavity and subsequently direct extension and intravascular spread into adjacent paranasal sinuses, cribiform plate and orbital structures. The infection then may extend to the meninges and cerebral structures.

Clinically, the symptoms and signs may be nonspecific, reflecting the local involvement. However, with full-blown cerebral phycomycosis the classic triad of (1) unilateral proptosis with cellulitis, (2) ophthalmoplegia with blindness and (3) paranasal sinusitis[30] in a diabetic patient with ketoacidosis should alert a physician to this diagnosis. Other clinical manifestations include blood-tinged nasal discharge, black necrotic turbinates, progressive lethargy despite adequate therapeutic management of diabetes, unilateral headache and focal neurological signs.[26]

The differential diagnosis includes bacterial sinusitis, cavernous sinus thrombosis, Wegener's granulomatosis, malignancy, bacterial CNS infection and aspergillosis. To make a diagnosis of phycomycosis, tissue involved with the disease must be cultured for the fungi. Histopathology of tissue with appropriate staining may also confirm this diagnosis. If oral or nasal mucosa appear to be invaded, scrapings from these areas prepared with potassium hydroxide (KOH) may show the broad nonseptated hyphae under light microscopy. Showing the presence of these characteristic hyphae in the appropriate clinical setting will make a presumptive diagnosis of phycomycosis. Serological tests for these organisms are not available and examination of the CSF will not be useful in establishing the presence of cerebral phycomycosis.

Treatment of cerebral phycomycosis is directed toward (1) control of diabetes mellitus or underlying disease, (2) local excision of the involved tissue and (3) institution of parenteral amphotericin B. The minimal cumulative dose of amphotericin B recommended has been 3 grams with renal toxicity being the limiting factor.[26] Despite these measures, the overall mortality has been exceedingly high. Only prompt recognition with early therapy and possibly the development

of more effective chemotherapeutic agents will cause the survival rate to improve in patients with this disease entity.

Viral Meningitis

TERRY YAMAUCHI, MD:* In 1925, Wallgren[31] characterized a syndrome of aseptic or benign meningitis. His criteria for the diagnosis of this entity include (1) the acute onset of illness with signs and symptoms of meningeal irritation, (2) pleocytosis, (3) absence of bacteria in cerebrospinal fluid, (4) a short clinical course without complication, (5) absence of any signs of parameningeal disease or systemic infection that might have meningitis as a complication and (6) absence in the community of epidemic disease that might be associated with meningitis. The clinical features of this syndrome are fever, headache, nuchal rigidity and lymphocytic pleocytosis.

Although there are a large number of viral agents capable of infecting the central nervous system, for the sake of brevity I will only discuss the most common agents associated with this syndrome. Of the viruses implicated, enterovirus and mumps virus account for 90 percent of the proven cases of aseptic meningitis.[32,33]

A seasonal variation is seen in aseptic meningitis caused by these agents. Most enterovirus-associated diseases occur during the warmer months of the year with peak months in Southern California being July, August and September. Mumps virus-associated central nervous system disease is more common during the winter and spring months.[34]

The signs and symptoms of viral meningitis may vary considerably from patient to patient. Fortunately, most of these illnesses are benign and self-limited. The first symptom is often headache of acute onset, usually described as retroorbital or frontal in nature. In children this is not always a major complaint, while in adults the pain may be severe enough to require sedation and analgesics. In contrast to headaches, fever may be notably elevated in children and only mild to moderately increased in adults. With some of the enterovirus infections, a diphasic or triphasic fever pattern has been described.[35] Concurrent with fever, a variety of other symptoms may occur. These include sore throat, lethargy, myalgias, nausea, vomiting, generalized malaise and nuchal rigidity.

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When meningeal irritation is suspected, the following physical signs must be sought: (1) *Nuchal rigidity*, the patient is unable to place the chin on chest, (2) *Kernig's sign,* pain occurs in the hamstring area with efforts to extend the flexed knee beyond 90 degrees and (3) *Brudzinski sign,* when one extended leg is passively flexed, a similar involuntary movement occurs in the other leg.

Other less commonly encountered symptoms of viral meningitis are photophobia, tinnitus, dizziness, chest and abdominal pain, paresthesia and convulsions.

The duration and intensity of these signs and symptoms are extremely variable. In most cases recovery begins within a week of the illness and is complete within the next several days to several weeks. In general, the younger the stricken person is, the shorter the recovery period is and the less severe the symptoms are. Recently, at the Western Society for Pediatric Research Meetings in Carmel, California, a group of investigators from Seattle presented some provocative data on the long-term follow-up of a number of children with enteroviral infections of the central nervous system.[36] The findings of this study suggested that children infected with enterovirus during the first year of life had significantly lower IQ's, smaller head circumferences and language impairments.

When considering the differential diagnosis of viral meningitis one must first contemplate other entities that may be potentially life-threatening disease processes and require vigorous, specific therapy. Bacterial meningitis must be ruled out as early as possible. The indiscriminate use of antibiotics has on many occasions made the diagnosis of viral versus bacterial meningitis difficult. There are several excellent review articles that well summarize this controversial problem.[6,7,37] When confronted with this dilemma, a physician has two choices: either treat the patient as having bacterial meningitis and administer intravenous antibiotics for 10 to 14 consecutive days or carefully monitor the patient for 12 to 24 hours off antibiotics and repeat a lumbar puncture.

Other infectious agents must also be considered in the differential diagnosis of viral meningitis. Tuberculous meningitis is often initially misdiagnosed as having a viral cause. In addition, mycoses such as Cryptococcus or Coccidioides, rickettsiae, protozoae and parasites must be ruled out before making a diagnosis of viral meningitis. Other systemic disease processes such as leuke-

mia, Hodgkin's disease, infectious mononucleosis, catscratch fever, pemphigus and benign infectious lymphocytosis can also mimic meningitis. Heavy metal poisoning, drug ingestion and head trauma are rare causes of meningitis symptomatology.

Laboratory findings play an important role in establishing the diagnosis of viral meningitis. In children, the peripheral leukocyte count may be variable, but a pronounced elevation of the leukocyte count with a polymorphonuclear response is usually seen in bacterial infections. Serological diagnosis depends upon a change in antibody titer when comparing acute and convalescent sera and therefore is not helpful early in the course of illness. However, certain diseases such as syphilis can be eliminated from consideration early with serological studies. Immediate examination of cerebrospinal fluid must be carried out in every case of suspected meningitis. Although the CSF in viral meningitis is usually clear in appearance, on occasion it is opalescent and may have greater than a 1,000 leukocytes per ml. The more usual range is 15 to 500 cells. The predominant cell type is mononuclear but early in the course of illness a polymorphonuclear cell response occurs. Other measures shown to be useful in the CSF of patients with viral meningitis include protein content (usually elevated but may be normal) and glucose content (usually normal and occasionally low). Hypoglycorrhachia has been reported in meningitis associated with both mumps and herpes simplex viruses.[8,9]

CSF samples should be cultured for viral agents as well as bacteria. In our viral diagnostic laboratory a presumptive diagnosis of enterovirus has been possible within 48 to 72 hours after lumbar puncture. Viral cultures from the nasopharynx and stools are also helpful in establishing a viral agent.

At present there is no proven effective specific therapy available for viral meningitis. The therapeutic use of deoxyribonucleic acid (DNA) inhibitors such as adenine arabinoside and cytosine arabinoside has been advocated in some severe viral infections, but the efficacy remains largely unproved.[38-40] Similarly, interferon inducers have been used experimentally for modifying viral infections.[41,42] More information is necessary before this type of therapy can become universal. Fortunately, viral meningitis is largely a self-limited disease and only symptomatic treatment is necessary. Analgesic-antipyrexic agents, maintaining adequate fluid and caloric intake are the basis of symptomatic therapy. More severe cases may require control of seizures, reduction of cerebral edema or increased intracranial pressure, and management of coma.

In addition to the general discussion of viral meningitis, some mention of herpes simplex virus (HSV) infection of the central nervous system should be noted. HSV infections have been recognized as an important cause of CNS disease in humans. Clinically HSV meningitis may be indistinguishable from meningitis due to other viral agents.[43] HVS infection of the CNS accounts for up to 19 percent of all cases of encephalitis[44] and often has extremely variable clinical features.[45] Generally, fever and headache are common early in the disease, but because the HSV can cause focal necrosis, early localized signs may also be present.[46] A patient with HSV encephalitis may present with drowsiness, confusion, disorientation, hallucinations and bizarre behavior. Although a wide variety of seizures may be seen, a common presenting feature is major motor seizures, often unilateral. Dysphagia and aphasia are frequently noted early in the disease. Sensory deficits such as paresthesias may precede the more severe CNS signs. Evidence of meningeal irritation may be present.

The lumbar puncture findings can also be extremely variable, from completely normal results to evidence of a pleocytosis, erythrocytes and elevated protein content. As mentioned earlier, low CSF glucose levels have been documented with HSV infections.[9] The pleocytosis is often a mixture of lymphocytes and polymorphonuclear cells, but may consist of lymphocytes only.[44]

Further diagnostic evaluation includes an electroencephalogram, brain scan and cerebral angiography. If findings on these tests make the diagnosis of HSV encephalitis probable, then a brain biopsy is recommended. Treatment for this disease with systemic antiviral agents or interferon inducers is now under investigation.

Reye's Syndrome

In 1963, Reye and co-workers described a syndrome of acute onset of encephalopathy with hepatic involvement and no other apparent clinical cause of the cerebral and hepatic abnormalities.[47]

Reye's syndrome is primarily an illness of children. Cases have been reported from a few months of age through adolescence.[48] In most of

these cases there occurred a prodrome of fever and upper respiratory symptoms followed by sudden, rapid central nervous system dysfunction and vomiting. Vomiting is such a consistent and early finding that at one time it was considered a necessary feature to clinically diagnose this syndrome. Delirium may present early in the course of illness and often progresses to coma. Seizures, as a manifestation of central nervous system dysfunction, occur in approximately 85 percent of clinically diagnosed cases. In many children mild hepatosplenomegaly and irregular respirations will develop. Often a rash is evident and represents an antecedent illness or precipitating factor. Varicella has been the exanthem most frequently described and this virus has been postulated as a causative agent in Reye's syndrome.[49,50]

Laboratory findings play a major role in diagnosing and guiding therapy in a child with this disease process. Liver involvement is characteristic, and serum levels of glutamic oxalacetic transaminase, glutamic pyruvic transaminase and blood ammonia are commonly elevated. Hypoglycemia is also a usual laboratory abnormality and the glucose concentration in the cerebrospinal fluid parallels the decreased values in the blood. Increased intracranial pressure has been another frequent finding, and some physicians have suggested monitoring and control of this as a valuable adjunct to treatment.[51]

Several viruses have been implicated in the cause of this unusual illness. Viruses which have been associated with this syndrome include Herpesvirus hominis, hepatitis, Coxsackie A, ECHO, adenovirus, reovirus, influenza viruses A and B, rubella, rubeola, parainfluenza and varicella.[52-57] For a virus alone to manifest infection in the human host as described, that agent would need to cause cerebral damage, and also produce a cellular toxin that interferes with intracellular metabolism leading to an accumulation of fat within the viscera.[58] Chang and co-workers[59] have reported a cytopathic agent they call "lipovirus," which produces a toxin capable of inducing fatty degeneration within cultured human cells.

For the present, the strongest link between a viral agent and Reye's syndrome involves the influenza viruses. Epidemiological studies have clearly shown an increase in Reye's syndrome associated with temporal and geographic areas within the United States and influenza B outbreaks.[53,60,61] Norman and co-workers isolated influenza B from the liver of a patient both antemortem and postmortem.[62] In a number of children stricken with this disease and in other family members there have been shown to be notably elevated titers of hemagglutination-inhibiting antibody to influenza B virus.[60] Influenza B infection within the community was documented concurrently by culture or serological techniques, or both.

The mortality ranges between 50 and 100 percent with this syndrome and most conventional forms of therapy have failed to influence the outcome.[47,63-65] More recently, encouraging results have been reported from various institutions in patients treated by hemodialysis, peritoneal dialysis, insulin and glucose infusion, and exchange transfusions.[66-68] In this hospital during the past eight months we have seen remarkable improvement in two children following repeated exchange transfusions. Further studies into the cause and pathogenesis of this disease process are needed. Currently a collaborative program to evaluate various therapeutic approaches is in progress and may aid us in treating this devastating disease in the future.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Polycillin®, Omnipen®, Totacillin®, Amcil®, Penbritin®, Principen®	*ampicillin*
Chloromycetin®	*chloramphenicol*
Fungizone®	*amphotericin B*
Ancobon®	*5-fluorocytosine*
INH®, Triniod®, Nydazid®	*isoniazid*
Myambutol®	*ethambutol*
Streptomycin	*streptomycin*
Cytarabine®	*cytosine arabinoside*
Adenosine arabinoside	*adenosine arabinoside*
Garamycin®	*gentamicin*

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Mycoplasma Pneumoniae Infections of Adults and Children

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Although the hallmark of Mycoplasma pneumoniae infection is pneumonia, the organism is also responsible for a protean array of other symptoms. With an increased awareness of the broad clinical spectrum of M. pneumoniae disease and the ready availability of the cold agglutinin and M. pneumoniae complement-fixation tests, interested clinicians will note additional clinical-mycoplasmal associations in their patients.

MYCOPLASMA PNEUMONIAE INFECTIONS are responsible for a considerable number of human illnesses. Although there is a vast amount of scientific knowledge available, there is still much confusion related to the spectrum and management of clinical diseases due to mycoplasmas. The purpose of this article is to review M. pneumoniae infections of children and adults in a way that will be useful to clinicians. Particular attention will be given to the less well-known manifestations of M. pneumoniae infections.

Definition and History

Mycoplasmas are the smallest free-living microorganisms; they lack a cell wall, they grow on lifeless media but require sterol for growth, and they are resistant to penicillin but sensitive to several other antibiotics.[1,2] Nocard and Roux[3] isolated the first mycoplasma species (now known as M. mycoides var mycoides) from cattle with contagious pleuropneumonia in 1898. Following this, numerous other mycoplasmas were isolated from cattle and other animals.[1] These other mycoplasmas were originally called pleuropneumonia-like organisms (PPLO). Presently, the term PPLO has been replaced by Mycoplasma; this is one genus of the family Mycoplasmataceae. Mycoplasmas have been isolated from many different animals including man. M. pneumoniae, initially called the Eaton agent, was identified in association with primary atypical pneumonia in 1944.[4] The Eaton agent was originally believed to be a virus until Marmion and Goodburn[5] in 1961 showed that it was identical to pleuropneumonia-like organisms. During the same year, Chanock and colleagues[6] administered a tissue culture grown Eaton agent strain to human volunteers and produced respiratory illness similar to primary atypical pneumonia. Although several different mycoplasmas have been recovered from humans (Table 1), the present report is only concerned with M. pneumoniae infections.

It is important to point out at the onset that in this report many of the clinical manifestations commented on were sporadic events and therefore may not necessarily have had a cause and effect

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TABLE 1.—*Mycoplasmas* Recovered from Humans*[7]

Respiratory tract	*Genital tract*
M. pneumoniae	M. hominis
M. orale (three types)	M. fermentans
M. salivarium	"T" - strains

*Listed by site of most common recovery.

relationship with M. pneumoniae infection. There is always the possibility of dual infection with the unrecovered infectious agent being responsible for the symptoms. It is the opinion of the authors, however, that these isolated cases should be included, with reservation, as they offer valuable points of reference for the observers. (See Figure 1 for clinical associations.)

Clinical Disease

Pneumonia

Incidence. The incidence of pneumonia due to M. pneumoniae in the general population is approximately one case per 1,000 persons per year. During epidemic periods, rates as high as three per 1,000 have been noted.[8] M. pneumoniae infections account for about 10 to 20 percent of all cases of pneumonia.[9-11] Since isolation rates do not vary greatly during the year, M. pneumoniae causes a greater proportion of pneumonia during the summer months when pneumonia due to other organisms is less common.[9,12]

The incidence of pneumonia due to M. pneumoniae is greatest in persons between the ages of 5 and 15 years while the percentage of all pneumonia attributable to M. pneumoniae is highest in late teenage and early adult years, when pneumonia due to all other causes is less common.[8-10,12] Pneumonia due to M. pneumoniae is uncommon in persons less than 4 or greater than 60 years of age.[9,10]

Symptoms and Signs.[9-14] Illness usually presents with the gradual onset of malaise and fever. Headache may also be a predominant early symptom. Cough begins after three to five days and becomes increasingly prominent. Initially nonproductive, the cough may later produce frothy, white or even blood-tinged sputum. Findings on Gram stain of the sputum show polymorphonuclear leukocytes with no predominant bacterial type evident. Gastrointestinal symptoms of anorexia, nausea and abdominal pain may occur. A pertussis-like syndrome with paroxysms of coughing has been described.[15]

Temperatures from 100° to 103°F (37.8° to 39.4°C) are common while higher temperatures are unusual.[19] Physical findings are generally of little aid in distinguishing M. pneumoniae pneumonia from that of other causes. However, as noted in Table 2, coryza is less common and lymphadenopathy more apparent in persons with

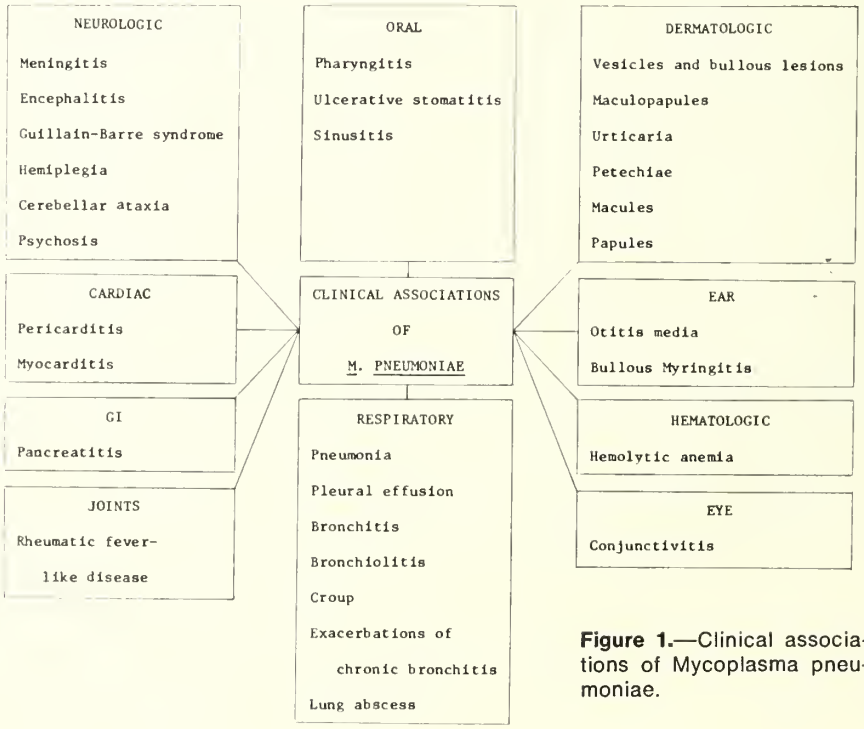

Figure 1.—Clinical associations of Mycoplasma pneumoniae.

TABLE 2.—*Relative Frequency of Selected Symptoms and Signs in Patients with Mycoplasma pneumoniae Pneumonia and Patients with Pneumonias of other Types*[11]

Findings	*M. Pneumoniae Pneumonia*	*Pneumonias of Other Types*
Cough	++++	++++
Headache	+++	+++
Pharyngitis	+++	+++
Sputum	+++	+++
Lymphadenopathy	+++	++
Conjunctivitis	++	++
Temperature ≥40°C	++	++
Coryza	++	+++
Pleuritis	±	+

M. pneumoniae pneumonia than in patients with pneumonias of other causes.

Dry rales are the most common finding on auscultation of the chest. They may persist for four weeks or more even though the patient is clinically improved. Symptoms of consolidation and friction rub may occur, substernal pain may be present but pleuritic pain is uncommon.

M. pneumoniae pneumonia is more severe in patients with sickle cell anemia,[16] with immunodeficiency syndromes[17] and with severe preexisting cardiorespiratory problems.[18,19] Although rare deaths have occurred, recovery is usual, although the clinical course is variable if untreated. Cough persists for three to four weeks in adults and usually for a shorter time in children,[8,10] while nonrespiratory symptoms of headache, myalgia and malaise may remit 7 to 10 days after their onset.

Roentgenography. Inconsistent relationships among the degree of symptoms, physical findings and results of chest roentgenographs are a hallmark of mycoplasma infection.[9,10,14,15,20] In many persons in whom significant infiltrates are seen on chest roentgenographs, there are no or minimal pulmonary findings. The radiologic pattern of M. pneumoniae pneumonia cannot be distinguished from other nonbacterial pneumonias.[21] Early in the course of M. pneumoniae pneumonia, the pattern is reticular and interstitial; subsequently, small patchy areas of superimposed consolidation are noted. Lower lobe involvement is most common and radiating infiltrates from the hilum are a frequent finding. Occasionally, lobar involvement is noted and pleural effusion also occurs.[22,23] In untreated patients, roentgenographic findings may persist for a month or longer.[24]

Routine Laboratory Data. The total leukocyte count in pneumonia due to M. pneumoniae is usually normal.[8,11] However, Turner and colleagues noted that the total leukocyte count was greater than 10,000 cells per cu mm in 13 of 22 children with M. pneumoniae infections; in 15 children, the differential percentage showed greater than 60 percent polymorphonuclear cells.

The sedimentation rate is frequently quite elevated.[25] Serologic tests for syphilis are occasionally noted to be falsely positive, serum cold agglutinins are frequently observed and antibodies to streptococcus MG antigen are found.[6,10,28,31] Serum IgM is frequently elevated while levels of IgG and IgA are normal.[30] The direct Coombs' test occasionally gives positive findings.[30]

Respiratory Disease other than Pneumonia

General. M. pneumoniae infections account for a significant amount of respiratory illness other than pneumonia.[10,13,20,31-35] Between 0 and 8 percent of all upper respiratory infections are due to M. pneumoniae. Pharyngitis is not uncommonly associated with M. pneumoniae infection; the peak incidence of M. pneumoniae pharyngitis is at 12 to 14 years old.[32] Bronchitis, bronchiolitis and croup have all been noted in association with M. pneumoniae infection.[10,13,33-35] Symptoms in these illnesses of children are usually mild.

In adults, exacerbations of chronic obstructive pulmonary disease have been associated with M. pneumoniae infections.[36,37]

Lung Abscess. Three patients with lung abscess in association with M. pneumoniae infection have been reported.[38,39] All three patients were males, aged 17, 24 and 45 years. All had two to four week histories of productive cough and pleuritic chest pain. In one patient, who was treated with tetracycline, there was dramatic improvement and on a follow-up roentgenograph six weeks later only minimal lingual scarring was seen. In the other two patients there was transient relief of symptoms during a week of therapy with tetracycline, but relapse occurred when the medication was discontinued. Both of these two patients eventually recovered although in neither was optimal antibiotic therapy carried out.

In a review of chest roentgenograms of 180 patients with pneumonia thought to be due to M. pneumoniae, four cases were found in which pneumatoceles were present, all clearing eventually.[21]

Otitis Media. Both acute otis media and the less common bullous hemorrhagic myringitis have been observed in M. pneumoniae infec-

tions.[9,10,20,33,35,40-42] In volunteer studies with tissue culture grown M. pneumoniae, Rifkind and associates[40] noted that in 13 of 52 subjects myringitis developed. Interestingly, myringitis occurred in 12 of 27 men without preinoculation of M. pneumoniae antibody and in only one subject with preinoculation antibody. The myringitis had an incubation period of six to nine days, was usually bilateral and was associated with throbbing pain. The appearance of the eardrum varied from mild infection to severe inflammation with edema. In five patients, hemorrhagic areas were noted and in two of these subjects serous-filled blebs which later contained blood were noted. Bullous myringitis has also been noted in several occasions with natural M. pneumoniae infections.[9,20,33,42]

The significance of M. pneumoniae infection in the etiology of common acute otitis media in children is unclear. In a study of 106 children with acute otitis media, Halsted and colleagues[41] were unable to recover M. pneumoniae from middle ear fluid. However, in 12 percent of the children there was serologic evidence of M. pneumoniae infection. Jensen and associates[35] noted laboratory evidence of M. pneumoniae infection in 47 of 79 children with otitis media. In this investigation, study children were selected because of suspected M. pneumoniae infection in a family member.

Sinusitis. Acute sinusitis is not an uncommon complication of a variety of acute infectious respiratory illnesses. However, clinically recognizable sinusitis was infrequently noted in persons with M. pneumoniae pneumonia.[29] However, when a radiographic search for evidence of sinusitis was made in 80 persons with M. pneumoniae infection, two thirds had sinusitis.[43] In these cases, the presence of sinusitis significantly prolonged the illness. In 30 patients with chronic suppurative maxillary sinusitis, Sprinkle[44] was unable to isolate mycoplasmas from antral lavage specimens.

Hemolytic Anemia

Clinical. Hemolytic anemia associated with M. pneumoniae infection has been reported on several occasions, but its occurrence is uncommon.[10,30,31,45-49] Hemolysis may be severe with a 50 percent reduction in hemoglobin occurring acutely. Severity correlates with high titers of cold agglutinins. A clinically inapparent, compensated hemolysis may also occur.[30]

Laboratory. In severe cases, the first evidence of hemolysis may be the rapid agglutination of blood in the syringe used for venipuncture.[47] Examination of a blood smear shows red cell agglutination, moderate spherocytosis, presence of polychromatic cells and at times erythrophagocytosis.[46-48] The serum bilirubin is usually between 1 and 3 mg per 100 ml. The leukocyte count may be elevated to a pronounced degree with a predominance of neutrophils, thereby confusing the diagnosis of M. pneumoniae infection. The direct Coombs test usually gives positive findings.[30,46-48]

Pathogenesis. The pathogenesis of acute hemolytic anemia in M. pneumoniae infection is unclear. *In vitro,* M. pneumoniae liberates peroxide which is a vigorous hemolysin.[31] However, in an organ culture system that is more akin to *in vivo* conditions, excessive peroxide liberation could not be shown.[50] Since the occurrence of hemolytic anemia has only been noted in association with notably elevated cold-agglutinin titers, it would seem that autoimmunity is of importance on pathogenesis. It would seem reasonable to suggest that mycoplasma organisms cause a temporary alteration of red blood cell membranes so that an autoantibody response occurs. In the patient studied by Fiala and co-workers,[45] bone marrow suppression also contributed to the anemia.

Prognosis. Hemolytic episodes are usually brief and self-limited, but have resulted in renal failure and death.[48] A beneficial effect of prednisone administration has been suggested but not adequately evaluated.[46] Since cold-agglutination may play a role in pathogenesis, it would seem wise to warm blood for transfusion to body temperature in patients with suspected M. pneumoniae infections.

Central Nervous System Disease

Clinical. A surprising spectrum of acute neurologic illness has been associated with M. pneumoniae infection.[10,11,15,18,28,34,48,51,52] The frequency of specific types of clinical involvement in 50 cases reviewed by Lerer and Kalavsky[51] is presented in Table 3. Combination involvement occurred in 36 percent of the cases. In 79 percent of the patients there was a history of antecedent respiratory illness. Neurologic illness occurred from 3 to 23 days after the onset of respiratory illness; the average interval was 10 days. The youngest patient was 6 years old and 47 percent were less than 20 years old. Of the patients less than 20 years old, 77 percent were males.

TABLE 3.—*The Frequency of Specific Clinical Involvement in 50 Patients with Neurologic Disease Associated with Mycoplasma pneumoniae Infection*[51]

Clinical Involvement	*Frequency (Percent)*
Generalized encephalitis	30
Spinal nerve roots	30
Meningitis	20
Cranial nerves	20
Focal encephalitis	16
Cerebellum	14
Psychosis	8
Spinal cord	2

Five patients were older than 50 years of age. This surprising number of cases in an age group in which M. pneumoniae infections are unusual would suggest a greater relative incidence of neurologic disease in older persons.

Prognosis. Five deaths have been noted, and major complications unrelated to the nervous system had played a significant role in all (for example, pulmonary embolus, pneumonia, sepsis).[51] In other patients there has been residual evidence of neurologic damage, mostly weakness but including hemiparesis, paraplegia and aphasia. Residua occurred more frequently in patients younger than 14 years of age who presented with focal encephalitis or radiculitis. There is no apparent correlation between severity of neurologic disease and height of cold-agglutinin or M. pneumoniae complement-fixation antibody titers.

Exanthem and Enanthem

Incidence. Exanthem in association with M. pneumoniae infection is more common than generally appreciated.[53,54] In a five year study in Seattle, 17 percent of 319 persons with M. pneumoniae penumonia had exanthem.[9] Copps and colleagues[55] noted that 11 percent of children with M. pneumoniae infections in a community outbreak in La Crosse, Wisconsin had exanthem and Feizi and co-workers[56] noted rash in a third of 40 patients in an outbreak in Scotland.

Clinical Findings. In a recent review, 20 well-documented cases of exanthem with M. pneumoniae were analyzed.[53] All but four of the patients were males and 19 of the 20 cases occurred in persons 4 to 20 years of age. Selected clinical findings are presented in Table 4. Skin manifestations were varied although in nine persons there were vesicular or bullous lesions, or both. Pruritis was noted in five patients. The duration of the rash was approximately seven days in all but one patient. All patients were febrile and the exanthem most commonly had its onset during the febrile period.

Enanthem occurred in 15 persons and it was severe in 10. In four patients severe conjunctivitis was present. Severe conjunctivitis only occurred in persons in whom there were vesicular or bullous exanthems, and in all four patients with severe eye involvement, generalized ulcerative stomatitis also was present. Interestingly, vesicular or bullous exanthems were not noted in females nor was ulcerative stomatitis or severe conjunctivitis.

In most patients, the spectrum of other symptoms was similar to those in patients with M. pneumoniae infections without exanthem. Only two of the 20 cases analyzed did not have pneumonia. The occurrence of an isolated rash as the single manifestation of M. pneumoniae infection is probably rare. In a study of 112 patients with suspected acute infectious exanthems, no significant antibody titers to M. pneumoniae were noted.[57]

Pathogenesis. The pathogenesis of exanthem in M. pneumoniae infection is unknown. In many patients, the enanthem-exanthem complex is consistent with the Stevens-Johnson syndrome. These findings might suggest an autoimmune phenomena perhaps with events similar to those inducing hemolytic anemia. It is important to point out, however, that in two instances M. pneumoniae has been recovered from blister fluid of patients with erythema multiforme;[58] in these cases, the exanthem could result from a direct effect of the infectious agent.

Many of the patients with M. pneumoniae infection and exanthem have received antibiotics before the onset of the rash. Therefore, the possibility of a drug eruption must be considered. In the analysis of the 20 detailed cases,[53] 12 patients had received antibiotics before exanthems occurred but six patients had a definite history of exanthem before antibiotic therapy. Although it is obvious that antibiotics cannot be incriminated in all cases, it is possible that M. pneumoniae infection intensifies the dermosensitive potential of certain antibiotics in a manner similar to that noted between the Epstein-Barr virus and ampicillin in infectious mononucleosis.

Arthritis

Mycoplasmas are a common cause of arthritis in animals other than man.[59] Eleven types of mycoplasmas have been clearly implicated in arthritides of seven different animals. Because many

TABLE 4.—*Major Clinical Findings in 20 Patients with Mycoplasma pneumoniae Infection and Exanthem*[53]

Clinical Category	*Number of Patients*
Distinguishing characteristics of exanthem	
Vesicular and/or bullous	9
Maculopapular	6
Macular	2
Papular	1
Urticarial	1
Petechial	1
Duration of exanthem	
<7 days	1
7 to 14 days	10
≥14 days	5
Not specified	4
Enanthem	
Generalized ulcerative stomatitis	10
Tonsillitis or pharyngitis	5
Conjunctivitis	
Severe	4
Mild	3
Pneumonia	
Yes	18
No	2

of the diseases in animals are suggestive of human rheumatoid arthritis considerable search for mycoplasmas in human arthritides has been done. At present, several mycoplasmas other than M. pneumoniae have been noted in association with rheumatoid arthritis. However, the results of studies to date are controversial and raise more questions than they answer.

Although it is highly unlikely that M. pneumoniae has a role in the cause of rheumatoid arthritis, joint manifestations have been noted during infections with this agent.[15,26,60-67] In five reports[60-64] ten instances of illnesses resembling rheumatic fever and associated with M. pneumoniae infections have been described. Seven of the ten patients were males. One patient was three years old, six were adolescents and three were adults. Most of the patients had a history of preceding respiratory illness including sore throat. When tested, sedimentation rates were found to be elevated. Seven patients had arthritis with swelling or effusion, and three had only joint pain. The knees were involved in all ten patients. In seven of the ten patients there was roentgenographic evidence of pneumonia.

One of the ten patients, a 71-year-old man, died with pericarditis and pneumonia. In the other patients, recovery was complete but after a prolonged period.

In 175 patients with M. pneumoniae pneumonia, George and co-workers[26] noted that 20 percent complained of myalgia, backache or arthralgia. In contrast, only 9 percent of persons with adenovirus pneumonia had similar complaints.

Cardiac Disease

Cardiac involvement during M. pneumoniae infection is unusual. In a series of 300 cases of M. pneumoniae infection, Hers[49] noted one patient with myocarditis. Grayston and colleagues[14] noted one 20-year-old girl with transient pericarditis in a study of 69 proven M. pneumoniae cases. A recent case report describes a 71-year-old man with the acute onset of an illness suggestive of rheumatic fever. At autopsy, effusions were found in the pericardial sac, pleural space, subdiaphragmatic area and in both knee joints. Mycocarditis and mitral valve lesions without Aschoff bodies were found. There was no laboratory or histologic evidence to indicate streptococcal infection, but pure cultures of M. pneumoniae were obtained from blood and from the pericardial effusion.[63]

Lambert[15] reported the case of a 50-year-old man who had acute pericarditis. This patient's initial illness required a three week stay in hospital; three months later, the patient experienced a second attack.

Pancreatitis

Mardh and Ursing[65] reported six instances of pancreatitis in patients with pneumonia due to M. pneumoniae. Two of the patients had only vague symptoms of pancreatitis but increased concentrations of serum amylase were noted. In three of the other four patients, the pancreatic symptoms began one to two weeks after the onset of respiratory illness; in one patient respiratory and pancreatic symptoms were concurrent. Diabetes mellitus developed in two patients and one of them died in a hyperosmolar, nonketotic, hyperglycemic coma.

Leinikki and Pantzer[66] noted four-fold rises in complement fixation antibody titer to M. pneumoniae in 18 of 56 patients with pancreatitis. None of these patients had pneumonia. Since the illnesses in these patients were so different from other M. pneumoniae infections, the authors suggested that perhaps a different but antigenically-related mycoplasm was the cause. Alternatively, they also raised the possibility of a false positive complement fixation test due to auto-antibodies to necrotic pancreatic tissue.

Communicability of M. Pneumoniae Infections

The rate of infection with M. pneumoniae is high in areas of close personal contact, such as families,[20,34,35,67,70] armed service camps[68,69] and fraternities.[71] In family studies, the attack rates vary between 64 and 71 percent among children and between 17 and 53 percent among adults.[20,67,70] In 74 percent of new Marine recruits four-fold antibody titer rises to M. pneumoniae developed during their 10 to 16 week training period.[18]

In contrast with families and military recruit training groups, the communicability in schools is low.[70] It is more usual for school children to become infected by neighborhood playmates than general classroom exposure.

The incubation period of M. pneumoniae infection is about three weeks.[67,70] Community epidemics due to M. pneumoniae are frequently protracted. Even in families, slow spread of the infectious agent is common and household involvement may continue for two months. Infection is most commonly spread by children of school age and by those patients who have a cough.[10,67,71]

Diagnostic Laboratory Tests

Serum Cold Agglutinins

The determination of serum cold agglutinins in patients suspected of M. pneumoniae infections is a simple and useful procedure. In pneumonias due to M. pneumoniae infections, cold agglutinins at a titer of approximately 1:32 will be present about 75 percent of the time.[25,31] Conversely, in patients with pneumonia and positive cold agglutinins, a specific antibody to M. pneumoniae will develop in 72 to 92 percent. In general, the cold agglutinin response correlates directly with the severity of illness.

Cold agglutinins have also been observed in 18 percent of adenovirus pneumonias in air force recruits[26] and in a variety of nonmycoplasmal respiratory illnesses of young children.[72] In general, the higher the cold agglutinin titer the more likely a specific infection is due to M. pneumoniae infection.

A rapid screening test for cold agglutinins can be done by an interested clinician.[73] In this test, four drops of blood are collected in a tube containing 0.2 ml of 3.8 percent sodium citrate solution. The tube is placed in ice water (0 to 4°C) for one-half minute and then examined for coarse agglutination by tilting the tube on its side.

Complement-Fixation Antibody Titers

Although there are several specific tests that can be used to measure antibodies to M. pneumoniae, the complement-fixation test is the only test readily available for routine laboratory use.[10] This test employs commercially available antigen and the results are satisfactory for usual diagostic purposes.

A four-fold rise in complement-fixation antibody titer is indicative of M. pneumoniae infection. Mycoplasma complement-fixing antibodies remain elevated for considerable periods so elevated single titers are of little value in disease diagnosis.[74] It is important to point out, however, that four-fold rises in antibody titer can occur in very short time periods. A second specimen collected within a week of the acute-phase serum will frequently show a four-fold titer rise.

Culture

With proper media and technique, M. pneumoniae is readily isolated from throat swabs of infected patients. However, M. pneumoniae is a relatively slow growing mycoplasma and therefore its isolation is of little use clinically. Serologic diagnosis is more practical.

Therapy

The therapeutic effectiveness of demethychlortetracycline in pneumonia due to M. pneumoniae was clearly shown in 1961 by Kingston and coworkers.[24] Since that time, several other antibiotics have been carefully studied and also found to be effective.[9,10,75] *In vitro* data indicate that M. pneumoniae strains are exquisitely sensitive to erythromycin, tetracycline, oxytetracycline and demethylchlortetracycline.[10] When expense and possible adverse drug reactions are considered, it would seem that the drugs of choice in M. pneumoniae infections are either erythromycin stearate or tetracycline hydrochloride.[9,10,75] Because of the adverse effect of tetracycline of dentition,[76] erythromycin is the drug of choice in children.

Despite the clinical effectiveness of antibiotics, organisms may still be recovered from throat cultures during and after therapy.[20,35] In the family situation, Jensen and colleagues[35] noted that the prophylactic use of oxytetracycline did not prevent infection of contacts but did render most infections asymptomatic.

Prevention

Inactivated M. pneumoniae vaccines have been tried with variable results. Mogabgab[77] reported significant protection following vaccination, whereas Smith and associates[78] noted that some vaccine recipients appeared to have more severe disease upon later exposure to M. pneumoniae. A recent trial with a live temperature sensitive mutant of M. pneumoniae gave encouraging results.[79] The mutant was avirulent in volunteers but appeared to stimulate resistance to subsequent challenge.

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Folk Remedies

Because of the number of Vietnamese people in the West, the use of folk remedies for illnesses may occasionally present unique diagnostic findings and should be recognized by practicing physicians. A 2½-year-old Vietnamese girl presented to the Emergency Room at Childrens Hospital of Los Angeles with a three to four day history of fever, cough and rhinorrhea. Positive physical findings included boggy erythematous nasal turbinates, mild erythema of the pharynx and a confluent petechial rash in the infraclavicular area of the chest bilaterally. A complete blood count showed a leukocyte count of 11,000 per cu mm with 60 percent lymphocytes and platelets within normal limits.

Several other Vietnamese children have been treated in our emergency room with similar rashes in the paraspinal and subscapular areas. Histories showed that these lesions are directly due to the popular practice among the Vietnamese population of using a coin to rub a mentholated compound vigorously into the skin in the infraclavicular, paraspinal and subscapular areas for approximately five minutes. The indications for this treatment include fever, rhinorrhea, cough and nonspecific symptoms in patients of all ages. Although less prevalent, coin massage with mentholated compounds may be used over the area of the biceps to treat abdominal pain.

The use of hyperthermia applied with a coin and mentholated compounds plays a major role in Vietnamese folk medicine and its external manifestations should be recognized.

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Important Advances in Clinical Medicine

Epitomes of Progress—Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Preventive Medicine and Public Health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Preventive Medicine and Public Health which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Clustering of Hodgkin's Disease

THE USE OF CLUSTERS of cases with a similar clinical presentation for the development and testing of etiological hypotheses has been a major tool of epidemiology at least since the time of Snow and his classic work on cholera.

Classically, clustering of cases in time and space has been observed for infectious diseases; the degree of "contagion" traditionally relates to the several factors including the virulence and mode of spread of the organism, the incubation period and period and degree of infectivity of the host and the number of susceptible contacts during the infective period. Attempts to transfer the concept of disease clustering formulated from the study of acute infectious disease to the study of chronic diseases, such as cancer, has led to considerable confusion and misinterpretation. Most of the problem has centered on attempts using the time space method to establish viral causes for three types of cancer occurring in children and young adults: leukemia, Burkitt's lymphoma and Hodgkin's disease. In one study, Alderson and Nayak evaluated the cases of 737 patients in whom diagnosis was made in Manchester, England, from 1962 to 1968. They found no evidence of clustering using Knox's statistical test, with a variety of space and time differences. Here the investigators were concentrating on the date of diagnosis, with the attendant and very unlikely assumption of a brief latency period. In another study, Kryscio and colleagues examined patients in whom Hodgkin's disease was diagnosed in Connecticut from 1940 to 1969. No evidence of clustering was found.

Clustering of Hodgkin's disease has also been reported among students of high schools. The most important of the latter was reported by Vianna and colleagues of Albany, New York. Working outward from an anomalous situation in which a small number of cases of Hodgkin's disease occurred in friends in an Albany high school, they "linked" 31 of 208 patients in whom diagnosis was made from 1950 to 1970. There were nine instances of possible case to case "spread" and 25 possibilities of case to contact to case transmission. Unfortunately, their control group was completely inadequate since it was chosen only for the linked patients rather than for the entire group. In addition, since any patient with Hodgkin's disease has a 20 percent or greater probability of contacting another patient with the disease over a ten-year period by chance alone, the findings were not, in fact, especially surprising.

Prompted by this report, Kinlen and his colleagues have recently completed a case-control study in Oxford, England. They identified all 97 patients under the age of 40 with Hodgkin's dis-

ease diagnosed from 1962 to 1971 in the Oxford area. This age restriction is based on the observation that transmission was most likely to occur between young persons. For each patient a matched control with a nonmalignant disease was chosen who had been admitted to a local hospital during the year the patient was diagnosed. Each person was then interviewed in depth to build up a chronological life history.

The results of this study showed a considerable number of links between patients, but no more so than among controls. For example, 12 pairs of patients went to school together, but the expected number based on the total data was 11.7 (with a standard error of 3.6). Another such investigation is currently under way in Connecticut.

Unfortunately, other interview studies with inadequate or even no control groups continue to be reported. One produced evidence showing that certain schools had a continuing, high incidence of Hodgkin's disease; another found a high rate of the disease in doctors, and a third showed a high rate in schoolteachers. Serious doubt has been thrown on all these results. The school report is suspected of being only a nonrandom sample of the data required to make such claims. The reported high rate in doctors is flatly contradicted by a much larger and more complete study on the mortality of British doctors. Finally, the apparent excess risk in schoolteachers has been proved to be an artifact of study design; the teachers had, in fact, a normal risk of Hodgkin's disease, which appeared high only in relation to their low rate of other diseases. These studies on contagion are of little if any scientific value and can only confuse and dismay patients with Hodgkin's disease.

None of the above examples provide convincing evidence of cancer "contagion." The attempts to equate a tendency toward clustering and contagiousness have, as earlier stated, tended to confuse the interpretation of and even discredit, the usefulness of cluster studies in cancer epidemiology.

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Drugs and Cancer in Humans

TO EVALUATE REPORTS that purport to link clinically useful drugs to the later appearance of cancer, one need consider the current usefulness of the drug, how restricted the circumstance in which it must be used is, and the severity and prognosis of the condition for which it is given, as well as the validity of the epidemiologic evidence, the quantitative aspect of the risk and the gravity of the neoplasm alleged to result.

In one category should be listed the large category of drugs which display laboratory carcinogenicity or mutagenicity *in vivo* or *in vitro* that do not obviously cause human cancer, but which have simply not been subjected to real epidemiologic testing. The list of drugs in this category gets longer by the day. It includes tertiary amines such as oxytetracycline and chlorpromazine, most cancer chemotherapeutic agents (including methotrexate, widely used for psoriasis), prolactin stimulators (such as phenothiazines), griseofulvin, iron dextran, metronidazole (Flagyl®) and progesterone. Few drugs (most notably isoniazid) have been subjected to enough epidemiologic study to be removed to a category of presumed safety.

Next must be listed a group of preparations which are believed to cause cancer in man, but which are not currently useful drugs. Radium and mesothorium were abandoned as therapeutic agents because they produced osteosarcomas and carcinomas. Chlornaphazine is no longer used in cancer chemotherapy because, like its industrial relatives, it produced bladder cancer. Only long after most physicians stopped treating pregnant women with diethylstilbestrol was it recognized that it would produce clear cell vaginal carcinoma at time of puberty in the daughters who were exposed *in utero* during the first few months of their existence. Inorganic arsenicals (such as Fowler's solution) produce unusual skin cancers (and possibly other cancers) when taken internally. Finally, long-term ingestion in quantity of proprietary analgesics containing phenacetin appears to produce, among other things, transitional cell tumors of the renal pelvis.

In another category must be placed those drugs that are generally agreed to produce cancer but nonetheless are still clinically useful and are used only in restricted circumstances, generally for serious conditions. Radioiodine given in high doses for thyroid cancer probably increases the

risk of leukemia. Clinically useful alkylating agents such as cyclophosphamide and melphalan seem to produce acute myelomonocytic leukemia in some of the long-term multiple myeloma survivors. Radioactive phosphorus given for polycythemia vera also increases the risk from acute leukemia. Treatment of patients with oxymethalone or methyltestosterone derivatives has produced hepatocellular carcinoma. Diethylstilbestrol given over long periods for gonadal dysgenesis appears to sometimes result in endometrial carcinoma. Finally, the regimen of immunosuppression or the renal transplantation in connection with which it is given, or both, appears to increase the risk from several types of cancer, most notably reticulum cell sarcoma and liver cell carcinoma.

The most difficult category to deal with consists of commonly used drugs that have not definitively been shown to be carcinogenic for man, but about which the question has been seriously raised. It has been suggested that diphenylhydantoin (Dilantin®) produces lymphoma, that amphetamines are related to Hodgkin's disease and that rauwolfia preparations produce breast cancer. In each instance, subsequent studies have failed to reproduce the original findings, and it seems unlikely that these effects, if real, are sizable. Case studies have linked chloramphenicol and other bone marrow depressants to the development of leukemia and the hypothesis is credible, but there is no epidemiological evidence in support of it.

Somewhat more credible evidence is available in support of the carcinogenicity of other preparations. Coal tar and creosote preparations may well cause skin cancer on sites of repeated application. Oral contraceptives have been studied extensively, and clearly do not increase the risk of breast cancer over the short term. Whether this will be true over the long term, particularly in young women who have many years of exposure, cannot yet be established. However, some oral contraceptive agents do seem to produce a small but real excess risk of liver adenoma, dangerous because of the tendency of the lesions to bleed. There is also some inconclusive evidence that endometrial cancer in younger women may be related to sequential contraceptive preparations.

At the head of the list must appear exogenous estrogens as used in the treatment of menopausal symptoms. Among the most widely dispensed of agents, estrogens have long been suspected of some carcinogenic action in man, but their full impact is only now becoming apparent. Several studies have indicated greater than a five-fold increase in the risk of endometrial cancer in estrogen users, and an apparent recent increase in the trend in incidence may reflect the wide use of these preparations. While the question of the carcinogenicity of estrogens for the breast is not yet resolved, it seems very unlikely that any effect of remotely comparable magnitude exists.

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Better Recognition of Minor Venereal Diseases

THE REPORTABLE venereal diseases are gonorrhea, syphilis, lymphogranuloma venereum, chanchroid and granuloma inguinale. Little emphasis in recent years has been placed on the diagnosis and treatment of the latter three, and, therefore, few cases have been reported.

The diagnosis of lymphogranuloma venereum should be based on both clinical findings and laboratory confirmation. The clinical course involves an incubation period of 3 to 21 days (usually 7 to 12 days). The lesion then appears as an evanescent, painless vesicle or papule at the site of contact, followed in 1 to 30 days by regional lymphadenitis in nodes draining the inoculation site. Dissemination via the lymphatics occurs. Progression of the disease may produce chronic buboes, elephantiasis, fistulae, strictures and esthiomene.

There is no good screening test for lymphogranuloma venereum. The Frei skin test usually does not become positive until 12 to 40 days after the appearance of the primary lesion. It usually remains positive for life and approaches a 70 percent sensitivity. The complement fixation test (LGV-CFT) is 90 to 95 percent sensitive and usually becomes positive one to three weeks after infection. Both of the above tests aid in

confirming the clinical impression. Immunofluorescence and neutralization tests more specific for lymphogranuloma venereum are currently being evaluated as diagnostic tools.

The current treatment of choice is with tetracycline. Sulfisoxazole may also be used. Therapy should be continued until a cure is achieved.

Chancroid has an incubation period of two to five days followed by a shallow, painful, soft, dirty ulcer at the point of contact. Multiple lesions are common, regional lymphadenitis occurs, and extragenital occurrence of the disease may be seen.

Diagnosis most commonly is made when the clinical presentation is consistent with chancroid and any one of the following features: (1) rugged serpiginous ulceration of the coronal sulcus; (2) severely erosive lesions, and (3) a classical unilateral bubo. Culture of the organism is often difficult. Gram staining or the use of Barritt's modification of Pappenheim's pyronin methyl green stain may be used on smears of ulcers or bubo aspirates with identification of organisms resembling Hemophilus ducreyi (diagnosis is presumptive). Fluorescent antibody staining, if available, is specific and sensitive. The ducreyi skin test antigen is no longer available.

The current treatment of choice is with sulfisoxazole. Tetracycline may also be used. Administration of both should be continued until effective cure is achieved. Streptomycin and kanomycin are reserved for resistant and erosive lesions. Buboes should be aspirated as incision and drainage is contraindicated.

Granuloma inguinale has a unknown incubation period with the estimate being 8 to 80 days. The clinical course is characterized by the insidious onset of a usually painless papule or nodule. This lesion erodes leaving a beefy red granular base. Lymphadenopathy may be present.

The diagnosis may be made by scraping the base of a lesion and identifying Donovan bodies using a Wright or Giemsa stain of the material. Tissue biopsy may also be done for identification.

The current treatment of choice is with either tetracycline or streptomycin. Administration of the medication should be continued until a cure has been effected.

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The Use of the FTA-ABS Test for Syphilis

THE FLUORESCENT TREPONEMAL ANTIBODY-ABSORBED (FTA-ABS) test is the most highly specific and sensitive test for syphilis and has generally replaced the TPI (Treponema pallidum immobilization) test. Its chief use is to confirm reactive reagin or screening tests for syphilis—such as the Venereal Disease Research Laboratories (VDRL) or rapid plasma reagin (RPR)—in order to distinguish between syphilis cases and "false positive" reactions. It is also useful in the diagnosis of late syphilis when the reagin tests may have become negative. Once positive it generally remains reactive for life, despite therapy, and therefore cannot be utilized to evaluate treatment. It is not appropriately used as a screening test for syphilis because of technical difficulties in making tests on a large number of specimens. The significance of a reactive FTA test on spinal fluid, when the VDRL is negative, has not been established.

The FTA-ABS test is generally reported to physicians as "negative," "borderline" or "reactive." Negative indicates no treponemal antibody present and occurs in incubating or early primary syphilis as well as in uninfected persons. Borderline test results are simply inconclusive and tests should be repeated. If results of a second test are still borderline and clinical data do not indicate syphilis, the patient should be considered not infected. Reactive FTA-ABS tests indicate presence of treponemal antibody, usually a syphilis infection, but in a small percentage of people a positive FTA-ABS may occur in the absence of treponemal disease. This situation most often is found in the presence of abnormal globulins in the blood.

The FTA-ABS is not a quantitative test, but in the laboratory the degree of fluorescence observed when the test is read is recorded as 1+, 2+, 3+ or 4+. The amount of fluorescence may vary on repetition of the test with the same sample of blood or on subsequent samples from the same person; therefore many laboratories do not report the degree of fluorescence for fear of confusing the physician. In general, however, a weakly fluorescent specimen is more likely to be a false positive than a strongly fluorescing one. When clinical features are not suggestive of syphilis in a patient whose FTA-ABS test has been reported as reactive, the laboratory should be asked to provide information on the degree of fluorescence

observed when the test was read. The weakly fluorescing reactive FTA-ABS should be regarded with considerable scepticism if there is no other evidence—serologic, clinical, historical or epidemiologic—of syphilitic disease.

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Unavoidable Vaccine Reactions

A 1974 JUDGMENT by a Texas Federal Appeals Court may seriously and adversely affect public immunization programs throughout the country. The plaintiff in the case was an infant girl in whom paralytic poliomyelitis developed two weeks after poliovaccine was administered to her at a local health department clinic in the spring of 1970. At that time an epidemic of poliomyelitis with over 20 cases was reported in an area of Texas close to the Mexican border. A number of expert witnesses testified that the child's disease was probably due to wild poliovirus circulating in the community. However, the court disregarded this testimony, and ruled against the vaccine manufacturer for failure to warn the infant's parents of possible vaccine complications. The Center for Disease Control estimates that one vaccine recipient-associated paralytic case occurs for every 11.5 million doses of poliomyelitis vaccine distributed in the United States. The court said that the manufacturer of an "unavoidably unsafe product" had a duty to warn the consumer of the risk in use of the product, no matter how slight the chance of injury. This case was appealed to the Supreme Court but the lower court ruling was upheld.

This legal decision requires that manufacturers directly inform each vaccine recipient of the possible complications attendant on use of their products. This decision has placed a burden on public or other outpatient facilities where nurses administer vaccines to groups of patients. The need to inform apparently does not, as a result of this legal decision, add an additional burden on private physicians, who should have a closer medical relationship and adequate communication with their patients.

As a result of the court ruling, national guidelines are being prepared on what information about rare vaccine complications should be conveyed to vaccine recipients attending public clinics and how it should be done. A few severe and unavoidable reactions will continue to occur even when vaccine recipients are informed about the risks involved. The question of compensation for these reactions is a difficult one, but needs to be answered equitably both for the patient and providers. To date, six European countries and Japan have plans under which the state provides compensation to persons adversely affected. It is hoped that a critical review of the present United States system (or lack of system) to compensate those who suffer severe adverse reactions will result in clarification and resolution of this problem.

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Recent Advances in Imported Disease

LARGE NUMBERS of American tourists travel to exotic parts of the world and imported disease should be a concern of physicians in this country.

In recent years imported civilian malaria has surpassed the number of military cases and any traveler presenting with chills, fever and headache must be considered possibly to have malaria. Chemosuppression, usually with chloroquine, should be recommended for all travelers to malarious areas. Typhoid fever should also be considered in a febrile traveler. Chloramphenicol and ampicillin resistant strains of Salmonella typhi are becoming more frequent and widespread worldwide and where this occurs, the treatment of choice should be co-trimoxazole, a combination of trimethoprim and sulfamethoxazole.

Perhaps the leading parasitic cause of diarrhea in travelers is Giardia lamblia, which is contracted worldwide and most particularly by visitors to the Soviet Union. A number of waterborne outbreaks of giardiasis have also occurred in this country. Typical symptoms include foul diarrhea, gas and bloating, and prevention should be directed to avoidance of untreated drinking water and fresh fruits and vegetables. The scourge of travelers, "turista" or travelers' diarrhea, has recently been found to be most likely caused by enterotoxin producing strains of Escherichia coli —and it is possible that prophylactic antibiotics

may be of benefit and that a specific vaccine could be developed. Intestinal helminths are not infrequently contracted both abroad and in this country. A new broad-spectrum anthelminthic, mebendazole, is highly effective and well tolerated, and is particularly useful against trichuriasis (whipworm).

Hepatitis A is much more frequently acquired abroad than in this country and is also more common than hepatitis B. Gamma-globulin prophylaxis should be recommended for all travelers to highly endemic hepatitis areas as this is a proven effective means of preventing or at the least greatly modifying hepatitis A. There have been no smallpox cases imported into this country in recent years and at this time the only country reporting smallpox is Ethiopia. Nonetheless, it is likely that proof of vaccination will be required for some time for entry into many foreign countries.

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Lest We Forget: Smoking Revisited

OUR READING MATERIAL, medical and otherwise, is increasingly filled with descriptions of newly recognized threats to our health. Not to detract from the importance of these, we should periodically put them in perspective by being reminded of the sheer impact of a danger which is surely the most important to be yet recognized, both because of its impact and because of its preventability.

Whatever the benefits, the costs of smoking more than one pack of cigarettes a day include, as a conservative minimum, the following:

- Huge (by factors of 8 to 12) increases in the risk from cancer of the lung, buccal cavity, pharnyx and larynx.
- Large (more than twofold) increases in the risk from cancer of the esophagus, bladder, liver and biliary tree, and pancreas.
- Increases in the risk from cancer at most other sites. Overall, the person taking up smoking probably increases his or her long-term risk (before 65) of cancer from about 12 percent to about 25 percent.
- Large (more than twofold) increases in the risk from chronic obstructive pulmonary disease, chronic bronchitis, and peptic ulcer. The lifelong increment in risk probably amounts to at least 1 to 2 percent.
- Most important of all, large (more than twofold) increases in risk from coronary heart disease. Men who smoke cigarettes increase their long-term risk of a premature (before age 65) major coronary disease event from about 8 percent to over 25 percent.

The sum of these increases in morbidity works out to be about a 30 percent chance of an unnecessary and premature serious disease. Whatever the influence on morbidity, the coldest and hardest fact is that the increase in the probability of premature death from any cause is such that smoking entails about a 20 percent chance of premature and unnecessary death.

Moreover, the dangers of cigarette smoking are even greater for persons already finding themselves at increased risk for other reasons. For example, risk from lung cancer is not measurably increased after exposure to asbestos in nonsmokers, whereas in smokers it is astronomically high. Smoking synergistically increases the coronary heart disease risk in hypertensive patients and those with elevated blood lipids.

Although quantitation is difficult, the practice of smoking also is costly to nonsmokers. Because of the foregoing, nonsmoker's insurance premiums are increased in direct proportion to the number of their fellow citizens who smoke. Some evidence suggests that smoking is detrimental to children *in utero* and to nonsmokers in the vicinity of smokers. It has been estimated that smoking is the most important cause of fires in buildings and of fire casualties. Thus some of the direct and indirect costs of accident morbidity and mortality (including fire insurance premiums) must be added to the total.

No doubt the list could go on, but it need not. The smoking of cigarettes is surely a formidable contender for the prize of biggest optional detriment to the quality of American life, and that fact must not be allowed to get lost in the discussion of newly recognized dangers, whether the discussions are between physicians, or between physician and patients.

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Rabies

EACH YEAR in California, more than 130,000 animal bites are reported to local health departments; of these, approximately 85 percent involve dogs. Even though the incidence of canine rabies in California is low, some 11 percent of the dog bites involve stray dogs and it is these exposures that impose the decision upon the physician of whether he should treat for rabies. The currently approved and commercially available vaccine for use on humans is DEV (Duck Embryo Vaccine). This vaccine, however, has poor antigenicity and some humans manifest sensitivity to the product. As a result of these deficiencies, two tissue culture vaccines, in developmental stages for a number of years, were tried on a group of 31 veterinary students at Ohio State University. Sixteen of the volunteers at random were given the Wistar product (WI-38), a human diploid cell culture, and the rest were given the hamster kidney cell culture (HKCC). Both vaccines were administered intramuscularly in 1 ml doses. The WI-38 product had a potency of 4, the HKCC had a potency of 2.1. Three injections were given over a four-week period. Blood samples were taken before each injection and two weeks after the last injection. High titres developed rapidly in all participants in the experiment with a rapid rise in titre within two weeks after the first injection and a slight increase after the second and third injections. In summary, the two tissue culture vaccines elicited a strong antibody response with minimum side effects.

Another relatively new product available commercially is HRIG (Human Rabies Immune Globulin), which has become available in the last year and a half. This product is intended for use in those persons who are suspected of being (or are) allergic to equine serum and who have incurred a bite or exposure to an animal of a high-risk species. Since HRIG interferes with development of an active immune response to rabies vaccine, the same precautions are advised as for the equine-antirabies-hyperimmune-serum concentrate; that is, seven additional injections of vaccine are required when either the equine or the human product is used. For example, if 14 injections of vaccine, plus boosters at 10 and 20 days following the 14th injection, are planned; then, with use of HRIG, 21 injections are advised—followed by boosters at 10 and 20 days.

The tissue culture vaccines are not available commercially, but in special cases can be obtained from the Center for Disease Control in Atlanta at the request of the California State Health Department in Berkeley. HRIG may be obtained in California from Cutter Laboratories, 2480 B Avenue, San Lorenzo, California 94580.

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Public Health Aspects of Botulism

BOTULISM IS A public health emergency. Whenever a diagnosis of this disease is suspected, local public health disease control officers should be notified immediately.

The production of botulism toxin requires anaerobic conditions, a pH range of 4.6 to 8.6, and time for the organism to multiply and produce the toxin. Toxin can be ingested via contaminated food or absorbed from a wound contaminated with the organism Clostridium botulinum. The toxins usually affecting man are A, B and E.

The incubation period averages 10 to 18 hours. However, it can be as early as five hours and has been reported as late as eight days. The onset will vary with the amount of toxin and individual susceptibility. Twelve hundredths (0.12) gamma of pure toxin is lethal for a 150 pound person.

The first sign of clinical illness is most often a vague feeling of weakness accompanied by general malaise. Visual signs occur next and may include blurring of vision, double vision and eyelid droop. A gradual bilateral symmetrical descending paralysis then occurs. There is no sensory loss in patients; rarely, if ever, is there a fever or elevated pulse (unless a superimposed infection is present), and usually there are no signs of gastrointestinal irritation.

The laboratory diagnosis is made via mouse toxicity testing using a sample of the patient's blood and extracts of the suspected food. The purpose of the testing is to determine which botulism toxin is active and which food is the culprit. Testing of the patient's blood should not play a part in therapeutic management of the patient. It also should not be done as an academic exercise.

If there is a suspicion of botulism, treatment should be started as soon as possible. Trivalent antitoxin (A, B, E) is available through health

department channels. The local health department will facilitate obtaining the botulism antitoxin. They will also contact all other exposed persons, collect all the implicated suspicious foods and facilitate the specific toxin diagnosis. If the patient's treatment with antitoxin is begun promptly and supportive therapy is available for respiratory distress and complications, the mortality rate usually will be less than 10 percent. If the patient survives, there usually will be complete recovery with no residual.

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Isoniazid

ISONIAZID HAS BEEN in clinical use since 1952 and is known to be one of the most potent bactericidal agents against tuberculosis bacilli. The drug is used either in combination with at least one other drug in the treatment of tuberculosis or as a single drug for preventive treatment of infected persons without disease.

For treatment of disease in adults, the recommended daily dose is 300 mg per day. Higher daily doses are not more effective and result in an increased frequency of toxic reactions. The dosage in children is 10 to 20 mg per kg of body weight per day. One of two additional drugs is administered with isoniazid to reduce the chance that drug resistant organisms will emerge during therapy. At present, it is generally recommended that chemotherapy for tuberculosis be continued for 18 to 24 months, although much shorter courses of therapy (perhaps 6 or 9 months) with certain drug combinations are currently under investigation.

Isoniazid also has been used successfully, in combination with streptomycin or ethambutol, for intermittent twice-weekly chemotherapy of tuberculosis. The adult dosage in intermittent regimens is 15 mg per kg twice weekly. Pyridoxine usually is given concomitantly. Intermittent therapy should always be preceded by an initial daily treatment phase. There is no experience with intermittent therapy in children.

For preventive therapy, the dosage for adults is 300 mg daily, and in children 10 mg per kg of body weight per day, for 12 months. Preliminary results of a current trial suggest that shorter durations of therapy may be as efficacious. While the incidence of adverse reactions including isoniazid-associated hepatitis is low, screening procedures are recommended before starting preventive therapy and monitoring at monthly intervals during therapy.

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EDITORIALS

A BICENTENNIAL EDITORIAL

The Western Journal of Medicine Salutes America—1776-1976

AMERICA IS OUR COUNTRY and most of us love it. Like most loved persons or things, it can be disappointing, exasperating or even infuriating at times. But who else, what else or where else is better? America is our country and we will surely continue to love it. It has yet fully to achieve its destiny. What can medicine do to help?

THE WESTERN JOURNAL OF MEDICINE's recognition of the bicentennial year is in three parts. First, a series of bicentennial editorials appearing throughout the year seek to relate medicine and events in health care to the state of the nation at this moment in its history. Second, this Bicentennial Issue hopes to project a sense of a continuum from medicine on the Mayflower, through the American revolution, and then the flow of pioneering America westward to provide the beginnings of medicine in the West. Lacking description in this issue, but well known to all, is the growth of medical science and innovation in medical care in the West which have made and continue to make notable contributions to the nation and to the world. And third, and perhaps reflecting some of the spirit of those physicians and others who have sought the good life in the West, this issue of the WESTERN JOURNAL begins a forum for a broadly-based discussion of what might be the relationships of medicine and health care to quality of life, something which seems to be coming within the reach of an ever-growing number of Americans and people elsewhere in the world.

In this bicentennial year medicine and health care find themselves in a central position in a rapidly changing America. This central position carries with it an opportunity to play an important and potentially even portentous role in helping to shape the future of our country. The WESTERN JOURNAL salutes America and hopes that the genius within medicine can and will rise to match this opportunity for leadership—not only to reduce the pain and suffering of those afflicted or to cure their ailments but to help make a better quality of life for all a lasting achievement of this great nation.

—MSMW

Medicine in the 2000's

THE STAGE already is beginning to be set for what medicine will be like in the twenty hundreds. It will be set by forces and trends now discernible and actually well underway, and also by events scientific, social, economic and political—which are, and always will be, quite unpredictable. It may be assumed that there will be much that is different. Perhaps we can glean something by attempting to identify some of the recognizable forces now at work and then see how they might affect medicine and health care in the 21st century.

- One may anticipate the further commingling of the concepts of patient care, or sick care, with prevention, or health care. Even now these are not really separable either in the knowledge base they require or in practice. Prevention will be accepted as a proper concern of medicine and it seems certain to be extended to address all aspects of ill health even when these have behavioral, social or economic causes.
- There will surely be continued expansion of medical science and technology. Exactly what this will be is quite unpredictable but that it will occur is not. It will bring about new kinds of specialization among health professionals and further interdependence among them. There will be a need for flexibility, adaptation, coordination and capability for change among all health professionals.
- There will be a limit on the portion of the gross national product allocated to health,

whether for education, research or service. There will be a cap on the dollars, an end to unlimited growth. This is probably at our doorstep now. The right to health care and to equality of care for all will be limited, as is already often the case, by judgmental decisions about how best to allocate finite resources. Our mechanisms for arriving at such decisions are now at best primitive and at worst nonexistent. Better mechanisms will be needed.

- One can discern a trend away from materialism and even from equality toward a more individual- or person-oriented society. Evidence for this may be found in the present emphasis on personal fulfillment (for example, "do your own thing"), rather than fitting into society's mold, and in increasing reference to something called quality of life for the one as well as for the many. It remains to be seen how deep or permanent this trend is to be, but it has already begun to have many implications for medicine and health care.
- It seems possible that just as the biological nature of man was finally recognized in the 19th century, the biological nature of human society will have been recognized in the 20th. The process seems well started with widespread rejection of the dogmas of many of our social institutions, an evidently more biological approach to living, and a growing recognition of modern society's responsibility to preserve a biologically healthy environment for man on what has been called "spaceship earth." Human behavior is an essential ingredient of all this, and of any human society, and it is reasonable to approach this as a function of biology—as is done with any other species in the animal kingdom. A logical consequence would be the development of a broadly based discipline of human biology as a basis for medicine and health care in the 21st century.

Given these trends and unpredictable events scientific, social, economic and political, what might medicine be like in the twenty hundreds? It seems inevitable that the scope of medicine, broadly defined, will embrace the care of the ill and the prevention of ill health whether of persons, of society, of the biological environment or of the genetic code of the human species. Also inevitably, medicine will be concerned with the delivery of health care and with how this is accomplished. The essential knowledge base will become broadly defined to include a biological understanding of health and its aberrations throughout the whole scope of a biological society. Whether this knowledge base will be called medicine, human biology or something else remains to be seen. It really doesn't matter. The effort must be to prevent unhealth and to cure it wherever it occurs. This is what medicine is really all about.

What will physicians be doing? There will be many other health professionals in virtually every aspect of health care. They can be taught to carry out almost every function of a physician, as is becoming evident today. In fact the question arises, is there any essential function of a physician which only a physician can do and which holds true for the whole scope of medicine? It appears that there is. It is the informed opinion of what is wrong, what will happen and what can be done about it. To carry out this function a physician must have a knowledge base in medicine; that is to say, he must have the knowledge of health and its disorders whether in the human organism itself, or in its behavior, or as it is affected by societal, environmental or species care influences. By definition this is the knowledge base of physicians and by virtue of its possession a physician is a physician. Practice skills for this essential function include adeptness as problem solver, teacher or advisor, advocate and sometimes as manager. Physicians may, and usually will, have other technical skills, but when they do they are functioning as highly skilled technicians rather than in the essential role of a physician.

What about other health professionals in the twenty hundreds? There will be many technicians and professionals with all sorts of skills. It is absolutely impossible to predict the number and kinds needed, although efforts are and will be made to do so. But what can be predicted is the need for flexibility and a capacity for health professionals to change to meet unanticipated needs and opportunities. As the knowledge base of medicine and health care is broadened to encompass many new aspects of what we have been calling human biology and its disorders, the knowledge and skills of physicians and other health professionals will be commensurately broadened. The educational system for health professionals also will have to become more broadly based and more flexible to respond readily to the needs of changing skills and changing roles.

In addition, there will need to be a mechanism for direction or governance within the system to

provide adequate professional guidance and advice for the allocation of always limited resources to research, to education and training, and to a wide variety of health care services. Wherever and however these decisions are made, it is essential that physicians be involved so that the knowledge base of medicine and human biology can adequately be brought to bear.

—MSMW

Mycoplasma Pneumoniae

THE DISCOVERY of Mycoplasma pneumoniae as the causative organism of cold agglutinin-positive primary atypical pneumonia and its identification and recognition as belonging to the genus Mycoplasma marked a major milestone in clinical investigation of the past three decades. Mycoplasma pneumoniae became the first mycoplasma species proved pathogenic for man. In their review article on Mycoplasma pneumoniae infection in adults and children in this issue of the WESTERN JOURNAL, Cherry and Welliver call attention to the importance of this organism as a human respiratory tract pathogen and emphasize its potential for involving other target organs, a finding which has emerged from recent clinical studies.

The sequence of investigative events that established the causative role of Mycoplasma pneumoniae in respiratory disease represented a classic exposition of Koch's postulates. It was only during the early 1940's that Eaton experimented with a then unidentified organism in sputum from persons ill with primary atypical pneumonia which caused pneumonia in cotton rats upon intranasal inoculation.[1,2] Convalescent sera from these ill persons neutralized the pneumonia producing capacity of the agent. Neither a virus nor a bacterium, yet apparently sensitive to broad spectrum antibiotics, the identity of the organism eluded Eaton and other investigators until the mid 1950's.[3] In the face of the skepticism of that decade, Liu and Eaton succeeded in infecting embryonated chicken eggs with the organism and then detected it in the bronchial epithelium by an indirect immunofluorescent technique.[4] Applying these procedures to assay specific antibody, they investigated an outbreak of primary atypical pneumonia among adolescents at a boarding school and showed rising antibody titers that were temporally related to the course of illness; cold agglutinins also developed in most of these patients.[5] Their studies provided the first evidence that this organism—which had become designated the Eaton Agent—was the cause of primary atypical pneumonia and encouraged other researchers to investigate its pathogenesis and epidemiology and the effectiveness of antibiotics in its treatment.

In rapid order Chanock and his colleagues studied the epidemiology of this organism, described the clinical features of pneumonia and showed the efficacy of a tetracycline analogue in its treatment, experimentally produced infection and pulmonary disease in volunteers, and eventually isolated the organism on agar and identified it as a species of mycoplasma.[6-10] In 1963, the Eaton Agent was named Mycoplasma pneumoniae.[11] The development of techniques for the measurement of specific antibody to Mycoplasma pneumoniae and its relatively easy isolation on special agar medium facilitated numerous studies of this unique infection during the ensuing decade.

Cherry and Welliver's article reviews the new information providing insight into the diversity of clinical manifestations caused by infection with this organism. Much has been learned of its pathogenicity since 1940, but we cannot be complacent. For example, the development of cold agglutinins in Mycoplasma pneumoniae infection represents an intriguing consequence of infection with this microorganism that is still not understood. Measurement of cold agglutinins affords a useful, nonspecific diagnostic test of limited scope since these antibodies do not develop in all ill persons. They can be found in about half of the patients with Mycoplasma pneumoniae pneumonia, usually in the more severely ill ones. In addition to cold agglutinins, patients with Mycoplasma pneumoniae pneumonia frequently manifest other unusual serological reactions including the development of anti-lung antibodies, antibodies to Streptococcus MG and false positive serologic tests for syphilis. Although the relationship of these serological phenomena to the pathogenesis of this pneumonia has not been clarified, these findings suggest that there might be an autoimmune component in primary atypical pneumonia.

Human cold agglutinins formed in response to Mycoplasma pneumoniae infection are 19S and are specific antibodies for the I antigen of the erythrocyte membrane; they contain both kappa and lambda light chains, unlike those occurring in chronic cold agglutinin disease, and they possess low reactivity with the I antigen of cord blood erythrocytes. Cross absorption experi-

ments indicate that cold agglutinin and Mycoplasma pneumoniae antibodies are distinct.[12] That the 19S but not the 7S component of Mycoplasma pneumoniae antibody can be absorbed with I red blood cell antigen suggests a common specificity of these Mycoplasma pneumoniae antibodies and cold agglutinins.[13] Although direct evidence is lacking for Mycoplasma pneumoniae containing I antigen or an antigenic configuration similar to I antigen, absorption experiments with antibody to this organism and I erythrocytes suggest that possibility. Thus anti-I-cold agglutinins might be expected to form as a result of direct antigenic stimulation.[14] This facet of Mycoplasma pneumoniae infections is rich with experimental possibilities which might provide clues to understanding the pathogenesis of Mycoplasma pneumoniae infection and the accompanying serological phenomena.

Since Mycoplasma pneumoniae causes acute respiratory tract disease, does it play a role in chronic respiratory diseases of man, alone or in concert with other microorganisms? That mycoplasma infections of domestic fowl and other animals cause serious and chronic respiratory diseases provides a basis for suggesting that mycoplasma infections of the human respiratory tract might have a similar consequence. In some patients with Mycoplasma pneumoniae pneumonia there are a protracted course, delayed resolution of radiographic findings and residual abnormalities of the lungs and pleura. In patients with chronic bronchitis, Mycoplasma pneumoniae infections produce exacerbations, with worsening of pulmonary function.[15] The importance of mycoplasma infection as a cause of chronic respiratory disease of man remains largely unexplored, but it also seems a highly productive and informative pathway to pursue. The recognition of Mycoplasma pneumoniae as the etiologic agent of primary atypical pneumonia, its identification as a Mycoplasma and the delineation of other diseases it can cause will encourage an era of further investigation rather than conclude one, as all important discoveries do.

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A Review of Illich's *Medical Nemesis*

AT A TIME when the governor of the most populous state, the leader of the "New Generation of Politicians," espouses the health philosophy of the newest charismatic guru, Ivan Illich, the medical profession and society should take a hard look at the guru's latest pronouncement, *Medical Nemesis—The Expropriation of Health* (Pantheon Books, Random House, 1976).

In Greek mythology, Prometheus was employed by Zeus to fashion men from clay and instruct them in the arts of living. He stole fire from heaven and for his presumption or *hubris* (overwhelming pride), he was chained to a rock to suffer everlasting torture. Nemesis engineered the gods' revenge on Prometheus and on all those mortals who aspired to more than mortal power. Thus Nemesis has demanded retribution from every nation of the ancient and modern worlds when hubris exceeds humility.[1] Illich argues that modern man's confidence in the curative magic of medicine amounts to hubris and that Nemesis has

taken her inevitable toll in the proliferation of diseases caused by medical procedures and poisons (iatrogenesis), in the growing burden of medical expenses to all societies (capitalistic and communistic), and in the loss of ability of individual persons and families to cope with the reality of pain, suffering and death—a loss that reduces the fitness for survival of the race as a whole.[2] "Nemesis for the masses is now the inescapable blacklash of industrial progress. Modern Nemesis is the material monster born from the industrial dream. It has spread as far and as wide as universal schooling, mass transportation, industrial wage labour, and the medicalization of health." Thus Illich brings into focus his overriding philosophy of anti-industrialization as written in *Deschooling Society* (1971), *Tools for Conviviality* (1973) and *Energy and Equity* (1974).

The crux of Illich's ideas are summarized as follows:

"Increasing and irreparable damage accompanies present industrial expansion in all sectors. In medicine, this damage appears as iatrogenesis. Iatrogenesis is clinical when pain, sickness and death result from medical care; it is social when health policies reinforce an industrial organization that generates ill health; it is cultural and symbolic when medically sponsored behaviour and delusions restrict the vital autonomy of people by undermining their competence in growing up, caring for each other, and aging, or when medical intervention cripples personal responses to pain, disability, impairment, anguish and death."

"The most dramatic medical interventions: radical surgery, dialysis, organ transplants add untold agony to the patient's life and use up most societies' resources at a rate all out of proportion to the benefit they provide." This seems easy to refute when one considers pacemakers, cardiac prosthetic valves, prosthetic hip joints, positive pressure breathing machines, ventriculocardiac shunts and many other examples—leaving out entirely the advances in such areas as infection control with antibiotics, blood products, hyperalimentation and anticonvulsants. One must not only consider the length of life but the quality of life judged by the productivity and comfort of the individual person as well as the burden to his family and to society as a whole. This "caring" function in distinction to the "curing" function enables physicians to relieve, to support, to rehabilitate, to make life not only tolerable but rich and useful even in the presence of continuing disease.

Illich states, "That in every society, the dominant image of death determines the prevalent concept of health." And, "The well being of men and women increases with their ability to assume personal responsibility for pain, impairment, and in their attitude to death." Thus, he concludes, "Pain, sickness and death are seen (tragically to Illich) as contributing less and less to the real quality of life. The editor of the *British Medical Journal*[3] perhaps puts it best: "Few having read the horrors of deathbed scenes in the 19th century letters and fiction (including Tolstoy's own Ivan Ilyitch) could agree that death then was a calm, natural event which has since been subjected to 'medicalization' robbing the modern individual of dignity at the end of his life."

While Illich is critical of medicine and doctors in general, doctors must be one of the most self-critical professions, constantly examining and challenging traditional beliefs. They are well aware of the limitations, knowing full well that the mortality of life is 100 percent.[4]

What, then, are Illich's solutions to the problem. He exhorts for a return to personal responsibility for health care and turning medical technology and professional activity over to laymen. He wants people to drop out and to organize for a less destructive way of life in which they have more control of their environment. He would shift full burden of responsible use of drugs and procedures onto the sick person and his next of kin. Legislation would define each man's right to his own health, subject only to limitations imposed by respect to his neighbor's rights. In other words, Illich suggests a step backward—but neither organic nor cultural evolution can retrace its steps. Without the destruction of industrial society and of millions of people, this is not possible in the real world.

Yet Illich makes points, which are coming into focus more and more, regarding the finite resources that each society has in caring for its people. Technological medicine, and its batteries of machines, has to be restricted. There is simply not enough money to make it feasible for all who might benefit from it. In fact, it is always being rationed and probably always will be because of the cost. Therefore, priorities must be developed and physicians must lead the way. When the public has been fully informed, it and the profession must decide what they want from medicine and

how much they are willing to pay for it. Then the professionals can tell them what they can, in fact, have for the money. Fully realizing the finite level of resources, an active program of health education becomes one of the dominant priorities that society must accept, concentrating on adjusting the individual person's habits and life-style so as to avoid factors known to predispose toward serious disease. If everyone would stop smoking, the incidence of cancer would go down by 30 percent in a generation; but how can this be accomplished?

Illich's style is difficult. He uses exotic language, confusing in phraseology and sentence structure. He believes that citing a reference for every thought somehow makes his statements more authoritative and scholarly, when in fact he does not hesitate to use his footnotes as documentation for the frankly biased opinions of others to support his own bias.[5] There are 634 footnotes in the 275-page volume. His arguments are on a high, abstract plane and when brought down to the reality of everyday care of the individual patient beset with his woes and problems, illnesses and death, they become obscure and not meaningful. Nevertheless, the book is the kind of stuff that social planners and politicians will leap upon because it means inaction and a step backwards. Consequently it must be understood for its possible ramifications in the future of American health care.

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CASE REPORTS

Refer to: Scotvold MJ, Sareen C, Ruvalcaba RHA, et al: Acanthosis nigricans associated with tuberous sclerosis. West J Med 125:70-72, Jul 1976

Acanthosis Nigricans Associated with Tuberous Sclerosis

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TUBEROUS SCLEROSIS is an autosomal dominant hereditary disease with variable expression. It is characterized clinically by mental retardation, seizures and numerous skin lesions—of which the most characteristic are the cutaneous angiofibromas mistakenly called "adenoma sebaceum." Pathologically it is characterized by multiple tumors and malformations involving the brain, skin and viscera. Various endocrinopathies have been described with tuberous sclerosis.[1]

The purpose of this paper is to describe the case of a severely retarded girl in which a diagnosis of tuberous sclerosis was made, and present the first reported association of acanthosis nigricans occurring with tuberous sclerosis.

Report of a Case

The patient is a 13-year-old white girl who is a resident of Rainier School, a State of Washington institution for the mentally and physically handicapped. She was born at term to a normal mother and father. Labor and vaginal delivery were spontaneous and uncomplicated; the birth weight was 7 pounds 10 ounces; and the neonatal period was unremarkable. Growth, developmental landmarks and language acquisition were normal until about 24 months of age when the parents noted the patient was becoming hyperactive and aggressive, and was progressively losing her speech. By 6 years of age, the patient did not speak and was unable to understand verbal commands. Seizures began at 12 months of age and were finally brought under control at 4 years of age with administration of phenytoin sodium (Dilantin®), phenobarbital and mephenytoin (Mesantoin®). Bilateral malar adenoma sebaceum papules became apparent between three and four years of age.

The patient was admitted to hospital at Seattle Children's Orthopedic Hospital and Medical Center at 5 years of age. On physical examination, she was found to be retarded and hyperactive. Small, discretely papular, slightly violaceous cutaneous angiofibromas, "adenoma sebaceum" lesions, distributed bilaterally on the malar area in a butterfly distribution were noted. There were

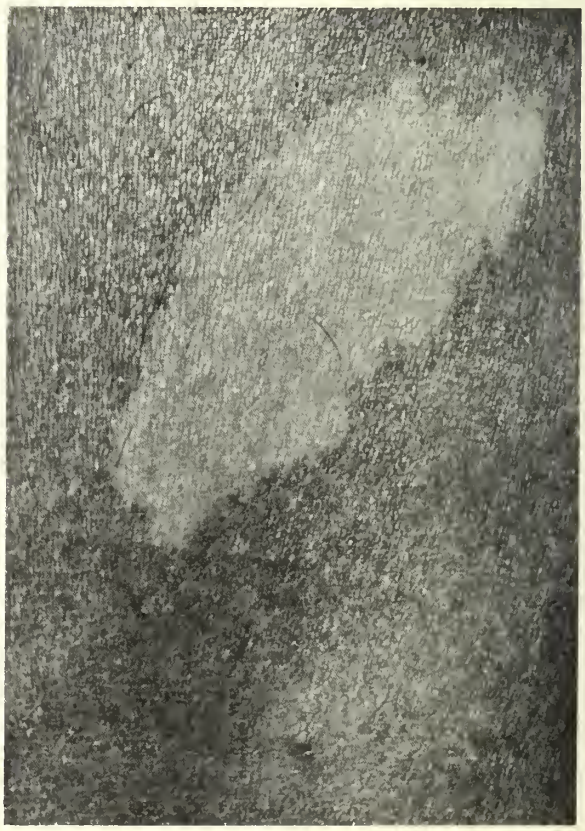

Figure 1.—Cutaneous patch of macular leukoderma.

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This investigation was supported in part by Public Service Grants 2TI-AM-5190 and AM-05250 and by the Department of Social and Health Services, State of Washington.

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numerous leukodermic macules, "ash-leaf shaped white macules,"[2] scattered over the trunk, three small tan-brown, slightly elevated shagreen patches on the buttocks, and many punctate, focal, yellowish scar-like spots on the choroidal part of the retina. Findings on an electroencephalogram were abnormal, showing a spike wave focus in the anterior temporal region. On a pneumoencephalogram, very slight dilatation of the right lateral and superior portion of the third ventricles was noted. No further follow-up studies were undertaken and no intravenous pyelograms or skeletal survey x-ray studies were made. She was discharged with a diagnosis of tuberous sclerosis.

Figure 2.—Adenoma sebaceum papules of the face in a butterfly distribution of cheeks.

Figure 3.—Acanthosis nigricans on the axillae.

At 6 years of age, the patient was admitted to Rainier School. On physical examination at 13 years of age, it was noted that she was not obese, that she was profoundly retarded and that her mental age was 14 months. Also noted were multiple large cutaneous patches of macular leukoderma (Figure 1); papillary fibromas on the neck; varying sized shagreen patches in the lumbosacral and buttocks area; multiple bilateral erythematous adenoma sebaceum papules on the nose, malar area and chin (Figure 2), and a bilateral axillary vault eruption characterized by a soft, velvety, verrucous hyperpigmentation that was compatible with a clinical diagnosis of acanthosis nigricans (Figure 3). There were no periungual or oral fibromas, fibromatous plaques or nodules on the head or neck, or poliosis (circumscribed gray hair) in the eyebrows, lashes or scalp.

A skin biopsy study of the axillary acanthosis nigricans lesion (Figure 4) showed striking epidermal papillomatosis and moderate hyperkeratosis, with no significant acanthosis or hyperpigmentation. The suprapapillary plates projected upward as discrete finger-like projections, each containing abundant keratin within the valleys formed by each projection.

Findings on baseline laboratory studies were all within normal limits. These studies included a complete hemogram and urinalysis; determinations of blood urea nitrogen, serum electrolytes, calcium, phosphorus, bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transami-

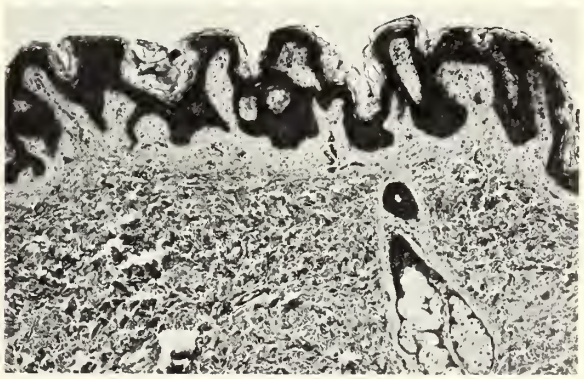

Figure 4.—Skin biopsy study of axillary lesion. Note the epidermal papillomatosis and moderate hyperkeratosis, with no significant acanthosis.

nase, serum glutamic pyruvic transaminase, cephalin flocculation and total plasma proteins with immunoelectrophoresis; x-ray films of the skull and chest bone age films; intravenous pyelogram; electrocardiogram, and electroencephalogram. Thyroid function, carbohydrate metabolism and the pituitary-adrenal axis were evaluated as previously reported.[1] The former both gave results within normal limits; however, the urinary steroid responses to intravenously given adrenocorticotropic hormone (ACTH) and metyrapone were found to be low, indicating a low adrenal reserve.[1]

Discussion

Acanthosis nigricans is a skin disorder of undetermined cause that can occur independently, as a result of a hereditary predisposition or as a cutaneous manifestation of any one of many underlying systemic or malignant diseases.[2,3] It presents clinically as a verrucous, hyperpigmented, hyperkeratotic cutaneous lesion that predominantly involves the folds or flexural areas of the skin in a symmetrical fashion. The normal skin markings are intensified, the cutaneous surface is studded with small papillomatous or nodular growths and the lesion has a striking soft, velvety texture. Although it has a predilection for the axilla, neck and groin, it can occur on the face, breasts, flexor creases of the elbows and knees, inner aspect of the thighs and mucous membranes.

Acanthosis nigricans has been found in association with underlying adenocarcinomas of the gastrointestinal tract, pancreas, prostate, ovary, breast and lung. It usually occurs in people over 40 years of age. It may be the first clinical expression of the tumor, and it usually runs a parallel course with the malignancy.[3,5] Acanthosis nigricans may be acquired as a rare autosomal dominant tract. As such, it may be present at birth, or it more commonly begins or is exacerbated at puberty. After puberty it generally becomes stationary or regresses.[4,6] Acanthosis nigricans can also occur as a part of several congenital syndromes. These include Bloom's syndrome, lipoatrophic diabetes, Wilson's disease and chondrodystrophy.[3,4,7] It has also been found in association with numerous metabolic and endocrine abnormalities including acromegaly; eosinophilic pituitary adenomas associated with gigantism; hypopituitarism secondary to a chromophobe adenoma; Cushing's disease; Addison's disease; Stein-Leventhal syndrome; hypothyroidism and hyperthyroidism; diabetes mellitus; benign encephalopathy, and pronounced obesity with nutritional, endocrine, or constitutional causes, and in patients treated with nicotine or oral contraceptives.[3,4,7-12] The degree of acanthosis nigricans associated with obesity appears to be proportional to the degree of obesity. The onset of acanthosis nigricans usually occurs at the time the obesity develops, tends to subside as the obesity subsides and usually disappears when the weight returns to normal.

The medical literature is replete with numerous and unnecessary divisions or subtypes of acanthosis nigricans.[2,3] These include malignant acanthosis nigricans and juvenile acanthosis nigricans. The latter has been further subdivided into benign acanthosis nigricans, acanthosis nigricans as part of several congenital syndromes, and pseudoacanthosis nigricans. However, acanthosis nigricans is one disease with the same clinical and histopathological manifestations no matter what other condition it is associated with. Therefore, if acanthosis nigricans is found in any patient, it should point toward a search for an underlying disease process. At this time, however, acanthosis nigricans should not be considered one of the expected cutaneous manifestations of tuberous sclerosis unless a significant number of patients with tuberous sclerosis are found to have acanthrosis nigricans.

Summary

This report describes the case of a 13-year-old severely retarded girl, the resident of an institution, in which diagnosis of tuberous sclerosis was made, and presents the first report of acanthosis nigricans occurring with tuberous sclerosis.

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Refer to: Parsons GH, Price JE, Auston PW: Bilateral pneumothorax complicating transtracheal aspiration. West J Med 125:73-75, Jul 1976

Bilateral Pneumothorax Complicating Transtracheal Aspiration

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TRANSTRACHEAL ASPIRATION (TTA) has been recognized as a valuable means of obtaining lower respiratory tract secretions in pulmonary infections since its original description by Pecora in 1959.[1] Findings in subsequent studies have attested to its value and relative safety.[2,3] Complications of the procedure, however, are not unknown[4] and include localized subcutaneous emphysema, bradycardia, aspiration of vomitus, transient hemoptysis, bleeding at puncture site, mediastinal emphysema, paratracheal abscess and death. Pneumothorax has not been a reported complication to TTA. We report a patient with respiratory insufficiency due to fat embolism in whom pneumomediastinum, pneumopericardium and bilateral pneumothorax developed as a complication of TTA.

Report of a Case

A 19-year-old man was well until two days before admission when he collided with a parked car while riding his bicycle. He was unconscious for several minutes, then was taken to a nearby hospital where a nondisplaced fracture of the midshaft of the left tibia was diagnosed and treated with a cast. The following day some scanty hemoptysis and mild shortness of breath were present. The morning of admission the patient was lethargic, confused, notably short of breath and was still having hemoptysis. He was transferred to Sacramento Medical Center.

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Submitted, revised, November 17, 1975.

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ABBREVIATIONS USED IN TEXT

TTA = transtracheal aspiration
IPPB = intermittent positive pressure breathing

On physical examination blood pressure was 150/70 mm of mercury, pulse 120 and regular, respirations 30 per minute and temperature 40°C (104°F). Multiple abrasions on the face and scalp with a left subconjunctival hemorrhage were noted. The funduscopic examination gave normal findings. On examination of the chest, distant breath sounds were heard but no rales, rhonchi or wheezes. The heart was found to normal except for tachycardia. Findings on examination of the abdomen showed no abnormalities. A left leg cast was present. On neurologic examination, the patient was lethargic but oriented, with hyporeflexia but without sensory, motor, cranial nerve or focal neurologic abnormalities. Result of a leukocyte count was 14,400 with 12 bands, 72 segmented neutrophiles, 11 lymphocytes and 5 monocytes. Hemoglobin, hematocrit, serum electrolytes, blood urea nitrogen and glucose studies all gave findings within normal limits. Findings on studies of arterial blood gases on room air showed oxygen pressure (Po_2) to be 43 mm of mercury, carbon dioxide pressure (Pco_2) 25 mm of mercury and pH 7.44. On a roentgenogram of the chest, diffuse patchy nodular consolidations throughout both lung fields were seen (Figure 1).

The patient was given oxygen by nasal prongs at 8 liters per minute to alleviate hypoxemia. To obtain uncontaminated lower respiratory tract

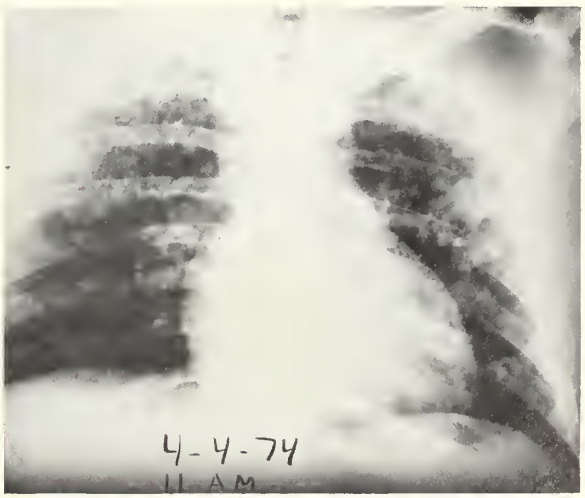

Figure 1.—Anteroposterior roentgenogram of chest on admission showing diffuse patchy nodular consolidations throughout both lung fields.

secretions for cultures, TTA was carried out with a plastic catheter (Venocath-14 Surgical, Abbott Laboratories) producing hemorrhagic fluid that subsequently grew alpha streptococcus, Neisseria catarrhalis, and Haemophilus species. On a repeat roentgenogram of the chest two hours after the TTA a pneumomediastinum and pneumopericardium were seen (Figure 2). Because no predominant organism had been seen on a Gram stain of the transtracheal aspirate, a transnasal fiberoptic bronchoscopy was done which showed only pink frothy material in the airways. No biopsies or brushings were done. Five and a half hours after the TTA one intermittent positive pressure breathing (IPPB) treatment was given. Six hours after the TTA had been done, the patient noted a sudden increase in shortness of breath with pronounced bilateral chest pain. On a roentgenogram of the chest a bilateral pneumothorax was noted (Figure 3). Chest tubes were placed bilaterally for closed intercostal drainage. The patient was intubated and mechanical ventilation was instituted. Fat globules had been seen in bronchial washings, spinal fluid and urine, suggesting a diagnosis of fat embolism. After treatment with steroids and low dose heparin the patient had an uneventful recovery with discharge on the 12th hospital day with no abnormalities seen on a roentgenogram of the chest.

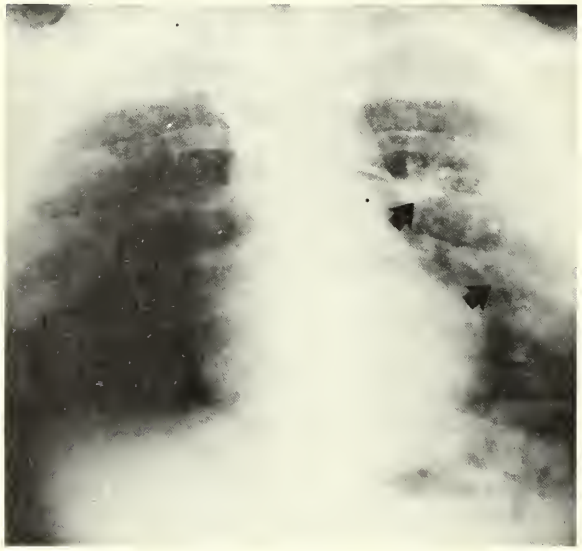

Figure 2.—Anteroposterior roentgenogram of chest two hours after transtracheal aspiration showing a pneumomediastinum and pneumopericardium (arrows).

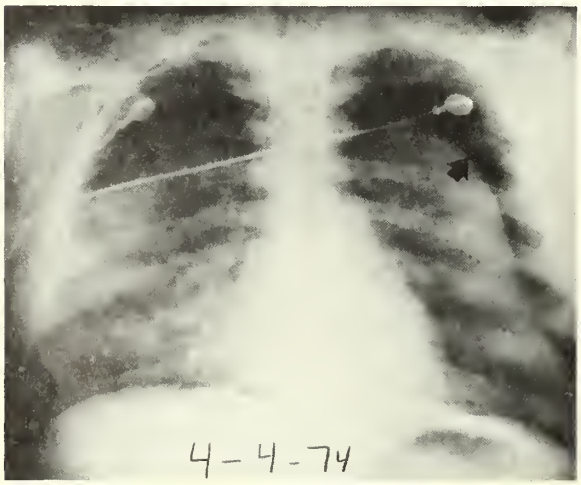

Figure 3.—Anteroposterior roentgenogram of chest six hours after transtracheal aspiration showing a bilateral pneumothorax (arrows).

Discussion

Pneumothorax following TTA has not been previously reported, yet its occurrence should not be unexpected in cases where pneumomediastinum developed. Pneumomediastinum and pneumothorax are known complications to tracheotomy, especially in children.[5]

The mechanism for its occurrence after tracheotomies, as suggested by Padovan and coworkers,[6] involves the entry of air through the cervical incision and its downward passage peritracheally into the mediastinum during inspiration. When significant pressure exists within these mediastinal air pockets, rupture into the pleural space is possible. Padovan's experimental work with cats suggests that hyperextension of the neck applies mechanical tension to the mediastinal pleura and favors bleb rupture with escape of air into the pleural space.

The patient described had no tracheostomy. A needle puncture of the cricothyroid membrane presumably allowed air to leak from the trachea and to gain access to the peritracheal fascial plane. It seems unlikely that room air could pass through the bandaged cutaneous needle puncture tract in sufficient quantity to produce a leak of this magnitude. Presumably the drop in pleural pressure accompanying inspiration favors air dissection down into the mediastinum. With a relatively noncompliant lung, larger drops in pleural pressure occur during inspiration and augment air passage into the mediastinum. The IPPB treatment may have contributed to air passage into the mediastinum. We assume in this case that the mediastinal air ruptured into both pleural spaces causing a bilateral pneumothorax.

A transnasal fiberoptic bronchoscopy was done to obtain tracheobronchial secretions for examination. This was carried out after the pneumomediastinum was recognized but before the pneumothorax developed. No brushings or biopsies were done. The procedure was tolerated with little coughing. We are unable to exclude the bronchoscopy as contributing toward development of the pneumothorax but the symptoms of sudden shortness of breath did not occur until several hours after the procedure.

The finding of mouth organisms in the culture of the TTA specimen probably indicates that the tip of the catheter was coughed into the pharyngeal area during the procedure. The authors do not want to defend the use of TTA or fiberoptic bronchoscopy in the management of this case. It should be noted, however, that at the time the procedures were done the diagnosis of fat embolism was not established.

Although TTA is recognized as a valuable diagnostic procedure in lower respiratory tract infections, it is not without complications. Where pneumomediastinum is present following transtracheal aspiration, clinical deterioration or sudden shortness of breath should alert clinicians to the possibility of pneumothorax.

Transtracheal aspiration should be included as another potential iatrogenic cause of pneumothorax.[7]

Summary

In a patient with pulmonary insufficiency secondary to fat embolism, pneumomediastinum, pneumopericardium and bilateral pneumothorax developed following a transtracheal aspiration. Air dissection down the paratracheal fascial plane with rupture into the pleural spaces bilaterally is the proposed pathogenic mechanism for this unique complication.

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Refer to: Blonde L, Witkin M, Harris R: Painless subacute thyroiditis simulating Graves' disease. West J Med 125: 75-78, Jul 1976

Painless Subacute Thyroiditis Simulating Graves' Disease

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SUBACUTE THYROIDITIS (DeQuervain's thyroiditis) usually begins with painful, tender thyromegaly, evidence of hypermetabolism and nonspecific symptoms such as fever, malaise, myalgias and arthralgias.[1] Subacute thyroiditis without pain or tenderness is described in surgical reports[2-4] but not emphasized in medical series.[1,5-8] This report describes four cases, collected over two years, of painless subacute thyroiditis with initial symptoms and signs like those of hyperthyroidism. In all four patients (three female and 1 male), painless thyroid enlargement, clinical hyperthyroidism, elevated serum thyroxine levels, normal or only slightly elevated sedimentation rates and suppressed thyroidal uptake of radioactive iodine were present initially (Table 1). None of these patients had ingested exogenous thyroid hormone, iodides or other medications. During subsequent observation, the goiters and laboratory abnormalities disappeared and the patients became clinically euthyroid with only symptomatic support.

Reports of Cases

CASE 1. A 19-year-old white male college student with no spontaneous complaints was seen for a preemployment physical examination. On examination, the thyroid gland was found to be enlarged to three times normal size and was firm but not tender. Findings from the physical examination were otherwise normal. Subsequent ques-

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Submitted July 28, 1975.

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tioning revealed a one month history of nervousness, heat intolerance, insomnia and a 5 kg weight loss, despite a good appetite.

A complete blood count was within normal limits with an erythrocyte sedimentation rate of 8 mm per hour (Westergren, normal for men is 0 to 10). Serum thyroxine by competitive protein binding was 14.3 μg per dl (normal 4 to 11 μg per dl). Resin T-3 uptake was 70 percent (normal 40 to 60 percent).

The patient was thought to have Graves' disease until the uptake of radioactive iodine (^{131}I) was found to be less than 2 percent at 24 hours (normal 10 to 30 percent). Treatment was deferred. Over the next four weeks the patient reported spontaneous clinical improvement but subsequently complained of fatigue, at which time a repeat test of serum thyroxine was found to be less than 1 μg per dl and administration of sodium levothyroxine (Synthroid®), 0.2 mg per day, was begun. Three months later, while still taking the medication, the T-4 and resin T-3 uptake were within normal limits. Thyromegaly had disappeared and the patient felt well. Administration of levothyroxine was discontinued. The patient was restudied two months later and was found to be euthyroid.

CASE 2. A 22-year-old white woman came to the emergency room because of palpitations and heat intolerance. During the preceding three weeks the patient had experienced nervousness, irritability, insomnia, heat intolerance and a 2.3 kg weight loss, despite good appetite. The patient said that there had been no neck pain.

The pulse was 110 beats per minute, blood pressure 140/70 mm of mercury. The skin was warm and moist to the touch. A fine tremor of the outstretched hands and lid lag were noted, but no other eye signs of Graves' disease. The thyroid gland was found to be enlarged to about 60 grams in size. It was firm in consistency and not tender. The remainder of the examination gave findings within normal limits.

The T-4 was 12.5 μg per dl with a resin T-3 uptake of 65 percent. Findings on complete blood count, Sequential Multiple Analysis (SMA) 12/60 and urinalysis were all within normal limits. Erythrocyte sedimentation rate was 22 mm per hour (Westergren, normal for women is 0 to 20). The uptake of radioactive iodine was less than 2 percent at 6 and 24 hours after administration. Titers of antimicrosomal and antithyroglobulin antibodies (Bio-Science) were within normal limits.

Over the next three weeks there was some regression of the thyromegaly. Serum thyroxine values fell to normal limits after three weeks and to less than 1 μg per dl after six weeks. At this time sodium levothyroxine (0.15 mg per day) was prescribed which resulted in the serum thyroxine value returning to within normal limits. Administration of the medication was discontinued after three months and the patient has remained euthyroid.

CASE 3. A 24-year-old white, married woman was evaluated for heat intolerance of six weeks duration, weight loss of 4.5 kg despite good appetite, and thyromegaly without associated pain.

The pulse was 120 beats per minute and blood pressure 130/60 mm of mercury. There were no eye signs of thyroid disease. The skin was warm and moist. There was a fine tremor present. The thyroid gland was enlarged to about twice the normal size and was firm but not tender.

The T-4 was 13.5 μg per dl; resin T-3 uptake, 63 percent. Uptake of radioactive iodine was 2 percent at both 6 and 24 hours. Complete blood count was within normal limits, with an erythrocyte sedimentation rate of 15 mm per hour (Westergren). Tests gave negative findings for antithyroglobulin and antimicrosomal antibodies.

The patient was given propranolol (Inderal®), 20 mg four times a day, but no other medications.

Over the next eight weeks the thyroid gland returned to normal size, administration of propranolol was discontinued and the patient be-

TABLE 1.—*Case Summaries—Painless Subacute Thyroiditis*

Case Number	*Age (years)*	*Sex*	*Goiter*	*ESR**	*Initial 24hr ^{131}I Uptake† (percent)*	*Initial Serum T-4‡*	*Final Uptake (percent)*	*Final T-4*
1	19	M	3×	8	2	14.3	..	8.0
2	22	F	3×	22	2	12.5	..	7.5
3	24	F	2×	15	2	13.5	..	8.4
4	13½	F	3×	6	2	15.6	27	6.4

*Erythrocyte sedimentation rate: Normal male = 0-10 mm/hr; Normal female = 0-20 mm/hr.

†Normal = 10-30%.

‡Normal = 4-11 μg/dl.

TABLE 2.—*Association of Pain with Subacute Thyroiditis*

Previous Reports	*Pain*	*No Pain*	*Total Patients*
Medical			
Schultz[5]	24	0	24
Volpe et al[6]	52	4	56
Vanderlinde et al[7]	13	0	13
Saito[8]	49	2	51
Surgical			
Woolner et al[2]	21	16	37
Stein et al[3]	23	13	36
Harland and Frantz[4]	<50%	..	27

came clinically euthyroid. Serum thyroxine was 8.4 μg per dl and resin T-3 uptake was 50 percent.

CASE 4. A 13½-year-old white girl came to the Ochsner Clinic because a surgeon advised thyroidectomy to treat an enlarged thyroid gland. She had had no irradiation to the head or neck as a child and had taken no thyroid hormone or iodides. She had noticed increased nervousness for two to three months, irritability and heat intolerance. There was no family history of thyroid disease.

The blood pressure was 120/70 mm of mercury; the heart rate varied between 100 and 84 beats per minute and there was a coarse tremor. There were no thyrotoxic eye signs. The thyroid gland was diffusely enlarged, three-fold on the left, and two-fold on the right, with no bruit. A grade I/VI pulmonic systolic ejection murmur was noted.

The serum thyroxine level was 15.6 μg per dl and the resin T-3 uptake was 59 percent. The thyroidal ^{131}I uptake was 2 percent at 24 hours, and the erythrocyte sedimentation rate was 6 mm per hour (Westergren). No therapy was instituted. Six weeks later the T-4 was 5.5 μg per dl, the ^{131}I uptake 27 percent at 24 hours and the erythrocyte sedimentation rate, 3 mm per hour. The heart rate was 72 beats per minute. The thyroid was enlarged two-fold diffusely with the right lobe now slightly larger than the left. Three months after the initial examination the thyroid gland was not palpable and the T-4 was 6.4 μg per dl. In this interval her weight had risen from 45 to 50 kg. She remained asymptomatic.

Discussion

The differential diagnosis in a patient with elevated serum thyroxine levels (corrected for protein binding abnormalities) would include: (1) autonomous diffuse or nodular toxic goiter; (2) thyrotoxicosis factitia;[9,10] (3) hyperthyrotropic hyperthyroidism[11] from hypothalamic, pituitary or ectopic sources such as choriocarcinoma, hydatidiform mole or testicular carcinoma; (4) struma ovarii;[12] (5) jodbasedow, that is, iodide-induced hyperthyroidism;[13] (6) functioning metastases from thyroid carcinoma,[14] and (7) subacute thyroiditis.[1]

In patients reported here there was no history of iodide ingestion or thyroid hormone exposure before the initial evaluations. The combination of thyromegaly and a very low thyroidal uptake of ^{131}I without known iodide exposure eliminated toxic goiter, hyperthyrotropic hyperthyroidism, and jodbasedow. It made the diagnosis of factitious hyperthyroidism unlikely. Subacute thyroiditis seemed the likely diagnosis and the subsequent spontaneous resolution resembled the course of more typical cases.

Whereas in most patients with subacute thyroiditis there are greatly elevated erythrocyte sedimentation rates which serve to suggest the diagnosis of symptomatic subacute thyroiditis, in these four patients that were either normal or only slightly elevated erythrocyte sedimentation rates.[1] In two of the four patients transient hypothyroidism developed. In both, euthyroidism without replacement therapy eventuated, and in all four patients thyromegaly resolved completely.

The incidence of asymptomatic subacute thyroiditis in surgical series is high compared with its incidence in medical reports (Table 2). Volpe and co-workers[6] reported that only four of their 56 patients with subacute thyroiditis had thyromegaly without pain or tenderness. The diagnosis in two was made only after examination of surgically removed tissue. The clinical presentation of the other two was not specified. Three cases somewhat similar to the ones reported here were described recently by Papapetrou and Jackson.[15] Thyrotoxicosis was present also in their patients; however, thyromegaly was absent in two of the three and erythrocyte sedimentation rates were not reported. Hamburger[16] reported that 13 of 29 patients with subacute thyroiditis had minimal pain or tenderness and provided descriptions of two. One had been exposed to exogenous iodides and the other had no thyromegaly. Erythrocyte sedimentation rates were not reported.

These cases show that subacute thyroiditis can occur in the absence of thyroid pain or tender-

ness and with normal or only slightly elevated erythrocyte sedimentation rates. The importance of measuring the uptake of radioactive iodine in patients with thyrotoxicosis is reemphasized here since the initial diagnosis of Graves' disease was questioned only after discovery of depressed uptake of radioactive iodine. Specific determinations of serum thyroid hormone levels do not allow distinction among the various causes of hyperthyroidism and therefore have not obviated the value of the radioactive iodine uptake test in assessing thyroid gland function.

All the present methods of treating thyroid gland hyperfunction involve some risk of morbidity to the patient. Therefore, specific antithyroid treatment should be deferred until the source of the hyperthyroidism has been determined. In all four of the patients reported here the goiter resolved completely and the patients became euthyroid with only symptomatic support.

Summary

Clinical hyperthyroidism, goiter, elevated T-4 and resin T-3 uptake values and depressed thyroidal uptake of radioactive iodine were present in four patients. This combination in the absence of a history of ingestion of iodide or thyroxine-containing preparations suggested the possibility of subacute thyroiditis, although the usually associated anterior neck pain was absent. Despite only symptomatic treatment the hyperthyroidism and goiter disappeared thus mimicking the clinical course of subacute thyroiditis.

These case histories emphasize the importance of the radioactive iodine uptake test in distinguishing among the possible causes of hyperthyroidism. Had this test not been carried out, a diagnosis of Graves' disease might have been made.

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LETTERS *to the Editor*

Medicine in a Changing Society

To the Editor: I read with interest your editorial "America in Process of Change" in the April 1976 edition [West J Med 124:329-330, Apr 1976]. I appreciated what you wrote, but believe that a fundamental point or two was omitted. It is apparent enough that America may be in a "process of fundamental change." However, I believe that in your analysis sufficient qualification is lacking so that changes that are occurring in the neighborhood, in the family and in the legal system are lumped together without real differentiation as to desirability from the "idea of limitless growth, unbridled competition." It seems important to me to try to decide which changes, real or contemplated, are desirable and which may not be desirable. Important in such deliberations is to understand the way that human beings actually behave and respond in a psychobiologic sense.

My theme, in answer to your statement, might be called "Human Nature as Applied to Social Reform." One gets the impression in your final paragraphs that changes are upon us, that we perhaps had better adjust to them and go along with them, and that Medicine had better somehow join the procession of adjusting and being a part of the change.

At least, you did not *say* that the 4,000 years of history must have taught us something about what is really good for people, how they preserve their freedoms, and what is apt to give them "personal fulfillment and quality of life." You have offered no opposition to the notion that these qualities, in addition to the purely physical necessities of food, water and bodily support, are not possible without hard work, self-discipline and personal involvement. You failed to note that personal fulfillment is possible in a wide range of social environments, and that these may include a moderate kind of competitiveness between people, a cohesive family, the sense of personal fulfillment coming from work to obtain the goods of life. Without earning, by some effort or work, one's goods, there can be little personal fulfillment or improved quality of life. The gift of these commodities, from whatever source, demeans their value. All around us are the social failures, replete with commodities provided for them, and yet asking for—demanding—more.

I would suggest then that human nature should be assessed by those who know it best, the physicians and the medical community at large. Between the public and private health practitioners, psychologists and psychiatrists, internists and other practitioners among people, there should be generated a good understanding of what human beings really need in order to be fulfilled, to be happy and to be in some way successful, and at the same time to benefit the world in some much larger way than their own lives alone. This, in addition to devising better approaches to pure physical and mental medicine, can be the contribution of physicians and indeed is among their prime responsibilities.

Peter M. Lewis, MD
Riverside, CA

A Changing America

To the Editor: In the past few decades, there have been truly fundamental changes in the United States affecting the values central to our civilization. [America in process of change (Editorial). West J Med 124:329-330, Apr 1976]. The spirit of our time is evident in the questioning of the judgment and integrity of previous generations in their ideas, conduct, institutions and decisions. There has been an almost unbelievable denial of any great amount of true wisdom in the past and almost total rejection of all that has been learned in the past, thereby opening the way for remaking man and society.

There is a climate of national "paranoia"—a distrust of past performance. The trials of the Rosenbergs and Hiss, and even the jury system, are looked upon as the debris of prejudice. A disturbing shadow is cast over the future performance of the CIA, the FBI and the police. Traditional morality is delegated to the garbage heap; permissiveness and the "joys of sex" are widely advertised but the connection to the "sorrows of sex" (such as venereal disease, divorce and abortion) eludes detection.

Attacks on business (such as it is now with

regulation and high taxes) are not recognized as the modern equivalent of classic socialist criticism. Euphemistic concepts to a future utopian society abound. The doctrine of "absolute liability" regardless of circumstances ("Somebody is injured, therefore somebody must pay")[1] governs our legal system and throws a very disturbing gloom over present day medical care. Political intervention is increasing and also the excesses of the environmentalists; the latter, both the natural beauty and clean air exponents and the carcinogen sleuths, are beginning to look somewhat ridiculous. Crime, violence, bombings, lawlessness and alcoholism become increasingly serious and the connection to lack of proper upbringing escapes us.

We live in a snarling era and the pretended "right" to this or that has become a national ethic. Personal responsibility is considered an aberration from the social norm. There is hardly a reminder of the obligation to provide for oneself and to limit aid to the truly weak, disabled and infirm. The well-to-do and the rich are lumped together with the needy and poor in such social programs as Medicare. The practice of monetary restraint and fiscal prudence is forgotten.

Policies and goals are not set by us but for us. We hear constantly that we are "living in a world of change." The progressives (liberals) are people "looking to the future" and "the future, as with all who try to protect themselves with this phrase, is their subjective feeling about the way things ought to go."[2] Just as the older philosophy had been defamed,[3] just as the older education, religion, economics and judicial system are defamed, just as history is denigrated,[4] the work of undermining our outlook and goals is proceeding and is mainly the work of those bent upon melioristic regimentation in the United States.

We are surrounded by topsy-turvy thinking. It isn't the people basically who are at fault, but the intellectual leadership. There is an unmistakable symptom of the "liberal syndrome": faulting society, not the individual, with her shady past.[5] It is time someone competent and knowledgeable, a philosopher perhaps (certainly not a psychiatrist), ponders the rise and the penetrating significance of our present generation of intellectual leaders who doubt the judgment and acts of former generations.

The pervasive influence of liberalism, however, is beginning to wane. The public is beginning to clamor for a halt to departures from our traditional concepts of social values and the proper role of government. The word "deregulation" is being voiced more frequently and widely. Moreover, it is astounding to hear the liberals of 1976 campaigning on Barry Goldwater's 1964 speeches[6] (FDR's political trickery of 1932?). Furthermore, according to the latest Gallup poll, "the public is overwhelmingly in favor of introducing instruction in morals and moral behavior in the nation's public schools."[7]

America *is* at the crossroads and the near future may determine whether we retain any notable semblance to what we were.

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Fault, No-fault, Justice and Patient Safety

TO THE EDITOR: Many Americans, eager to "initiate" tort reform and solve the problem of how to compensate the "no negligence" medical liability case, still behave like isolationists. While we talk about no-fault medical liability insurance, New Zealand has already put such a system into effect. While Californians now plan the "first" commission to determine the medical malpractice universe, the French have annually defined theirs, subclassifying it according to specialty. Currently, for example, the 60 cases per year of medical malpractice affecting French anesthesiologists represent only 5 percent of the total number of potentially compensable anesthetic accidents recorded by Le Sou Médical, the largest French medical liability insurance company.

It thus might do us some good to look at how other nations approach this international problem. According to reports presented at the World Medical Association meeting in Paris, March 1975, for example, the Japanese have worked out an intriguing compromise between fault and no-fault insurance. Since 1973, if the Japanese physician is found to be at fault, he must pay up to

the first million yen out of his own pocket. He cannot have insurance for this risk, although he is covered for amounts over this. (If no fault is found, presumably the government pays.) In this system, the local medical societies first review all cases in their own Dispute Settlement Committee. The briefs are then studied by the Survey Committee of the Japanese Medical Association and the Tokyo Marine Insurance Company, the most important of the four companies in Japan that share responsibility for malpractice insurance. The cases are then sent to a Deliberation Council, composed of leading physicians and lawyers. Its decisions are usually respected by the insurance companies and physicians. In the event of a frivolous case, a law suit is always sought. This discourages those who would abuse the system by trying to get an easy, out-of-court settlement.

Perhaps a similar compromise between fault and no-fault liability insurance will best balance justice with patient safety and security in America.

ALAN T. MARTY, MD
Los Angeles

Certification of Physicians' Assistants

TO THE EDITOR: I am writing in reference to the article on physician's assistants that appeared in the March issue [Oseran LS: Physician's assistants in California—A Socioeconomic Report of the Bureau of Research and Planning of the California Medical Association (The Health Care Team). West J Med 124:258-263, Mar 1976], and specifically a statement which appears on page 261 of that article. It reads, "To receive approval for practice in California, a PA must 'successfully complete' the Primary Care Physician's Assistant Examination developed jointly by the National Board of Medical Examiners and the American Medical Association in 1972, and administered by the National Board."

Currently, and since 1975, the National Commission on Certification of Physician's Assistants has been responsible for administration of that examination, and in subcontract to the National Board of Medical Examiners carries out that task.

We appreciate your help in correcting the error, and will be glad to offer any further information if needed.

HENRY R. DATELLE
Assistant Director
National Commission on Certification of Physician's Assistants
Atlanta

Our Far Flung Readers

TO THE EDITOR: I am writing you from the upper Amazon Valley where I am working among the head-hunting Shuar Indians. Our dispensary is far from any medical library or other source of medical information.

I tell you all this because I am in desperate need of keeping up-to-date. I remember seeing in some medical libraries copies of THE WESTERN JOURNAL OF MEDICINE. Could you send me a sample copy and information relative to a subscription?

THOMAS BROWN, MD
Medical Director
Dispensario Medico
Mision Salesiana Sevilla Don Bosco
Morona-Santiago, Ecuador

The Swine Influenza Controversy

TO THE EDITOR: The current crisis generated by the possible occurrence of the A/1918/swine/New Jersey influenza outbreak this fall and winter borders on the ridiculous. I cannot imagine what combination of factors has contributed to the government endorsed and sponsored program to inoculate the entire United States population, but we are ignoring many facts which may make this go down in history as a massive boondoggle. The effort will be expensive, will result in unnecessary illness from the vaccine itself, and is, ultimately, without real medical justification, no matter what names are behind the project.

As we in medical practice know, the "flu" is not a killer. The 548,000 flu-related deaths in the United States during the 1917 through 1919 epidemic were due—as have been all flu-related deaths since—to complications, mainly bronchopneumonia, lobar pneumonia, viral pneumonia and other forms of lower respiratory-tract infection. As we also know, a patient with multiple chronic diseases (such as chronic obstructive lung disease, congestive heart failure, diabetes) is extremely vulnerable to secondary infection of any type. When these patients contract an influenza-like illness, it often tips the scales and throws them out of control. It is for this reason that we as physicians have been giving such high-risk patients annual influenza inoculations. Of course, we cannot always anticipate what influenza will strike our community, and thus the antigen-

specific vaccines often are of little avail, as with this year's A-Victoria outbreak.

It also must be pointed out that prior to the 1940's there were no antibiotics, and influenza complications such as severe pneumonia were difficult or impossible to treat effectively. If the patient did not have the strength to overcome the onslaught of influenza plus pneumonia, he or she could end up with a fatal illness. Younger individuals who pursue their normal activities despite persistent cough and fever, rationalizing with "I just have the flu," are still in for severe respiratory infections, often requiring hospitalization. And now we have the further problem of heavy cigarette smoking, which comprises an especially deadly triad: chronic bronchitis, influenza and bronchopneumonia. But, looking at the total picture, now that we have many effective antibiotics, flu-related deaths are not as prevalent as they were several generations ago.

The third factor in this current controversy is the fact that most children should not be given influenza injections. The American Academy of Pediatrics has never recommended immunizing children against influenza routinely. The cumulative effects of repeated flu injections (annually, of course, as the virus undergoes transformation) is not known, and may not be known for decades. Therefore, many school children without chronic respiratory disease, will be unnecessarily immunized against the A/1918/swine/New Jersey virus. In ten years of pediatric practice, I would estimate that over 90 percent of children brought into the office with "flu" have some form of bronchial infection. Influenza illness in the community, when acquired by children, rapidly accelerates into lower respiratory tract infections. Therefore, when the term "flu" is used in connection with these infections, I feel the term is being misused.

The fourth, and perhaps the most significant factor, is that a drug which was developed in the early 1960's by du Pont is available for both the prophylaxis and treatment of A_2 influenza. This drug, amantadine hydrochloride (Symmetrel®), gives approximately 80 percent protection when taken prophylactically, and about the same percent of effectiveness when given early in the course of influenza syndromes.[1,2] It has been widely used all over the world, and in the United States since 1966. In the Soviet Union it has been used for prophylaxis since the A-Hong Kong influenza pandemic of 1968 and 1969. Russia not only has purchased over 10 million doses from du Pont to use during the next flu season, it also is modifying the molecule in search of more effective analogues, such as rimantadine.[3]

The drug is administered in capsule or syrup and is virtually without side effects in most individuals. For prophylaxis, I use a dose of 100 mg per day during the peak month or two of influenza in the community. For treatment of early, noncomplicated influenza, I use 100 mg twice a day in adults and children over age 9, for a one- to two-week course.

Amantadine hydrochloride, if taken by paramedical personnel, physicians, dentists and hospital staff members, would offer somewhere in the range of 80 to 85 percent protection against any of the A_2 variants which have come along in the past decade. Every significant influenza outbreak in recent years has been an A_2 variant: Asian, Hong Kong, London, Port Chalmers, A-Victoria and now A/1918/swine/New Jersey. There is some early investigation which shows *in vitro* sensitivity to amantadine hydrochloride in the case of this A/1918/swine/New Jersey strain.[4] In all probability, it is a variant of the A-Victoria strain which was also evident in the Fort Dix population.

The concept behind the vaccines is that they must be antigen-specific, must anticipate the next year's influenza strain and must be given prior to the actual outbreak of influenza in the community. The versatility of amantadine hydrochloride is that it can be given as soon as the outbreak hits the community (in Southern California, the A-Victoria did not arrive until February and March, 1976); it can be given for weeks or months, depending on the length and severity of the outbreak; it gives at least the same degree of protection as the vaccines, and it can be used for treatment of uncomplicated A_2 influenza syndromes with remission of most symptoms within 24 to 48 hours.

Dr. Jonas Salk stated in a recent article in *The Los Angeles Times* that one good reason to proceed with the mass immunization program is the fact that a 19-year-old Fort Dix recruit died from viral pneumonia.[5] Dr. Salk's work in virology cannot be challenged, but we must scrutinize the death of this young man: first, he collapsed during a night march; second, the A/1918/swine/New Jersey virus was recovered from throat culture;[6] third, the direct cause of death was viral pneumonia.

The total picture is not that influenza can be fatal, but that multiple factors, combined with or triggered by influenza, can cause morbidity and mortality. In this case, the triad was influenzal infection, exhaustion from the march and viral pneumonia. There may have been other factors which, as yet, have not been revealed. Certain questions would arise in the mind of any physician investigating such a death.

While we do not have a cure for viral pneumonia, supportive care and other modalities can often result in recovery, when the patient is not overwhelmed by multiple disease entities. It might be useful to point out (for the sake of further investigation) that in our local hospital, we used amantadine hydrochloride for treatment of viral pneumonia during the London flu outbreak of 1973 and 1974. Four patients failed to respond to various antibiotics, both as out-patients and during their hospitalization. All four cases responded clinically to amantadine. I cannot draw any final conclusion here, and other areas of inquiry remain, such as treatment of viral pneumonia with amantadine hydrochloride plus antibiotics.

Physicians have been reading about amantadine hydrochloride in the literature for many years, but have been reluctant to try it because of the lack of sufficient promotion by du Pont and Endo (which now handles the distribution). We have the Food and Drug Administration and the Center for Disease Control (CDC) to thank for that. The CDC is still telling American physicians to use "bed rest, aspirin and fluids" to treat uncomplicated influenza.[7] The media faithfully echo this refrain with every new flu outbreak. I wonder how many people needlessly die because they fail to seek medical attention solely because this wonderful advice is drummed into them annually! Some of these individuals are at home attempting to treat pneumonia with aspirin and fluids. By the time they do see their physician, they have severe respiratory disease, and many have to be hospitalized. An aura of helplessness surrounds each influenza outbreak, so that people are actually discouraged from seeking medical attention for early influenza.

The Food and Drug Administration is still preventing any advertising of amantadine hydrochloride other than for the treatment of Parkinson's disease and syndrome, and for the prophylaxis of A_2 (Asian) virus strains.[4]

While physicians in Russia and in other countries are no doubt amused at our enthusiasm over the annual influenza immunization ritual, they go on using amantadine, rimantadine and perhaps other equally effective antiviral agents in both the prophylaxis and treatment of the A_2 influenza syndromes.

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Comment*

DR. CHANIN properly draws attention to several important issues regarding influenza and the current program to immunize most Americans. This is a truly massive undertaking, and the decision to proceed can and should be challenged not only on the points he raises but on many others (such as effectiveness of the proposed vaccine, duration of immunity, administration to pregnant women, relationship of the current swine influenza virus to the agent involved in the 1917 through 1919 pandemic).

With respect to the projected epidemic, there is really only one indisputable fact—nobody really knows what is going to happen. Accordingly all of our arguments, pro and con, about the future are reduced to opinion. On the other hand there is a great amount of information available from the past, particularly with respect to influenza, the first virus to be reproducibly isolated.

I am not sure that Dr. Chanin quite appreciates the clinical differences between the Spanish flu of 1917 through 1919 and influenza since that time. The greatest pandemic the world has ever known is estimated to have involved 500 million people and to have killed 20 million, 548,000 of whom were Americans. Those who died were not preadolescent children or the aged, but young and middle-aged adults, women (nonsmokers in 1918)

*The Editors referred Dr. Chanin's letter to Richard Leonards, MD, chairman of an ad hoc subcommittee of the CMA Scientific Board concerned with swine influenza and the proposed use of vaccine.

as well as men. The disease killed rapidly—in 24 hours to a few days. The carnage lasted only a brief six to eight weeks, completely overwhelming medical personnel, hospitals and supplies. There is an interesting account of personal recollections of the pandemic by four living American physicians in a recent issue of *Medical World News*.[1] There are those who contend it won't happen again. It has already happened; and until we have a complete understanding and control of the factors that produce influenzal pandemics it may happen again.

Dr. Chanin's point about children is well taken. A recommendation from the American Board of Pediatrics will be forthcoming. The vaccine is being evaluated in children at this time.

From his comments I suspect Dr. Chanin regards viral pneumonia as a complication similar to secondary bacterial pneumonia rather than as part of the primary pathology, differing only in severity.

The utility of 1-adamantanamine is overstated. The A_2 strain is substantially different from the A-swine-New Jersey strain. In our current understanding one is not a variant of the other. There are no clinical studies of amantadine with respect to this latter virus; therefore, its *in vivo* effects are completely unknown. Although the prophylactic actions against the A_2 strain are well documented, the therapeutic effects are less clear. There are no controlled studies involving adamantine in severe influenzal illness even of the A_2 strain. Some respected authorities are of the opinion that it is useful. Amantadine is not tolerated by many people due to gastrointestinal, neuropsychiatric and cardiovascular toxicities. It is not advised for pregnant women, a specific group hard hit in the Spanish influenza pandemic. So far there are no available analogues less toxic or more effective. Apart from the above, I do believe there is a value to amantadine, and I hope it will be available as a backup for those unvaccinated or for those whom vaccination fails to effectively protect should an epidemic develop.

Despite the uncertainties of whether there will be an epidemic, or whether the vaccine will work, I intend to be vaccinated myself, to see to it that my family is vaccinated and to recommend vaccination to my staff, patients and friends.

I do not see this campaign as a political ploy of bureaucrats, but rather as a difficult decision forced upon responsible and knowledgeable men who could not live with the possibility of another Spanish influenza epidemic. There is a lucid discussion of several additional aspects by Dr. Louis Weinstein in a recent issue of *The New England Journal of Medicine*.[2]

RICHARD LEONARDS, MD
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Trauma Rounds

Chief Discussant
PAUL EBERT, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Ebert P: Cardiac injuries (Trauma Rounds). West J Med 125:85-87, Jul 1976

Cardiac Injuries

EDWARD VERRIER, MD:* The case for presentation today is that of a 27-year-old black man who was brought to Mission Emergency Hospital unconscious. No history was available. On physical examination, the patient was somnolent, diaphoretic and had pinpoint pupils. Blood pressure was 80/40 mm of mercury and there was peripheral vasoconstriction. The neck veins were palpable but were not considered distended. Naloxone hydrochloride (Narcan®) was administered and immediately the patient became arousable and coherent. He then complained of abdominal pain and it was noted that a small, 1 cm high, epigastric stab wound was present. Lung fields were found to be clear bilaterally. There was a normal sinus rhythm and heart sounds were described as clear. The abdomen was soft and bowel sounds were present, but there was tenderness to palpation in the epigastrium beneath the stab wound.

Hematocrit was 41 percent, urine was clear on analysis and findings on an x-ray film of the chest were interpreted as essentially within normal limits with a slightly elevated left diaphragm. The cardiac silhouette was unremarkable.

A central line was placed. Central venous pressure was shown to be 37. Shortly thereafter vital signs deteriorated further and the pulse was barely palpable. Pericardiocentesis was attempted. This was productive of approximately 25 ml of nonclotting blood and there was some temporary improvement in circulatory function. Central venous pressure remained high and peripheral vasoconstriction was pronounced with a blood pressure of about 90 systolic.

The patient was taken to the operating room a short time later and under general anesthesia a left thoracotomy was carried out. Approximately 250 ml of clotted blood was evacuated from the pericardium. The patient had a small—0.5 cm—laceration of the right ventricle, which was sutured. Postoperatively the patient has done well and was discharged on the sixth day after operation.

DONALD D. TRUNKEY, MD:† *We are privileged today to have Dr. Paul Ebert, Professor and Chairman of the Department of Surgery at the University of California, San Francisco. Dr. Ebert, using this case as a starting point, would you discuss cardiac injuries?*

PAUL EBERT, MD:‡ This case makes some very interesting points. When the patient first arrived in the emergency department, hypotensive and in compensated shock, it was unclear what the exact cause was. The initial response to administration of naloxone hydrochloride was encouraging, yet he continued to remain in shock, and the epi-

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gastric stab wound was noted. This stresses the importance of a careful complete physical examination. It is well documented that slow blood loss into the pericardium may occur in such patients and the blood becomes defibrinated and puddles in the posterior pericardium. This may not have profound clinical effects immediately, but as the effusion and amount of blood increase the effects become obvious.

When one reviews trauma to the heart, there is a broad range of injuries to consider. Penetrating injuries can be fairly straightforward or insidious, such as the one that was presented today. When the laceration is small, tamponade may be minimal because the leak can seal, bleeding cease and the injury not be recognized. Another type of injury results when the blood loss is continuous but slow. The pericardium in these circumstances may accommodate quite a large volume before sudden decompensation occurs. The classic studies done by Dr. James Issacs have been repeated many times since. He infused increasing amounts of fluid into the pericardium of a dog and showed that up to a certain point there is no change in pressures in the right side of the heart. Then, with an addition of 5 to 10 ml, sudden decompensation occurs with pronounced impairment of venous return to the right side of heart. It is this last small amount that causes the dramatic changes in hemodynamic measurements.

It is the potential for a sudden change in hemodynamic status that can sometimes lead initially to misdiagnosis. Examination of the neck veins may show only slight distension. The patient may be hyperventilating and it may be difficult to differentiate between tension pneumothorax and pericardial tamponade. If pericardiocentesis is done, a small amount of fluid may be obtained and there may be dramatic improvement in the patient's condition. One can be misled into thinking that other resuscitative measures rather than aspiration of the small amount of fluid led to recovery. However, just a small drop in the filling pressures of the right atrium and ventricle may cause a dramatic increase in cardiac output.

The response to fluid resuscitation in itself may be misleading in determining tamponade. Patients in whom there have been massive lacerations of the heart usually die at the scene of the trauma. The patients who survive cardiac injuries are those in whom tamponade occurs and the rate of hemorrhage is slowed. When these patients are resuscitated in the emergency department, their conditions usually improve initially leading to the assumption that volume loss was a problem. The point I wish to make is that tamponade can often be a very difficult diagnosis to make based on clinical, radiographical and even angiographic findings. Clinicians simply must have a high index of suspicion when shock occurs secondary to a penetrating injury that may involve the chest.

Dr. Trunkey: *Dr. Ebert, would you describe your method of doing pericardiocentesis?*

Dr. Ebert: The best way to carry out this procedure is to insert the needle in the left subxiphoid area at an angle of 45 degrees, aiming for the left shoulder. I personally prefer to have the needle connected to the V lead of the electrocardiograph with an alligator clamp. As one advances the needle, a QRS complex is displayed on the electrocardiogram. When the needle touches the epicardial surface, the QRS immediately reverses polarity and becomes a giant complex. By using the electrocardiogram as a guide, the needle can be adjusted so as to avoid entering the ventricular cavity, thus assuring that any blood aspirated is from the pericardium and not from the ventricle. I prefer to use a plastic needle with an inner metal cannula. When one reaches the pericardial cavity, the inner cannula is withdrawn and the plastic needle can be left in place to evacuate as much blood as possible. Once the diagnosis has been made by aspiration, I personally prefer to take the patient to the operating room, carry out thoracotomy and correct the lesion. The expectant treatment of patients with pericardial tamponade leaves a lot to be desired since the condition of such patients can deteriorate suddenly as previously mentioned. Just a slight increase in the amount of fluid can cause an acute and dramatic fall in cardiac output, such as was shown in the case presented today. Repeat aspirations with needles run the risk of injury to the coronary circulation.

A Physician: *What is the role of cardiopulmonary bypass in treatment of cardiac injuries?*

Dr. Ebert: It is advantageous to have cardiopulmonary bypass available but the chances of needing it are not more than one out of every 25 injuries. The major thing that bypass offers is that it facilitates repair of a coronary artery, should this have been injured. Bypass can be instituted, the heart fibrillated and with a quiet field the

coronary artery can be easily repaired. It should be remembered that the patient survived coronary artery injury and reached the hospital. If the injury involves the distal half of the coronary artery and the patient is doing well, ligation rather than repair is simpler and perhaps safer.

DR. TRUNKEY: *Dr. Ebert, would you comment about blunt traumatic injuries?*

DR. EBERT: There seems to be an increasing incidence of blunt cardiac injuries; however, the diagnosis is usually missed. One should have a high index of suspicion for this when an injury such as that produced by a steering wheel has occurred. Myocardial injury can be documented by findings on an electrocardiogram and one may see changes similar to those of acute myocardial infarction. It is also possible to note pericardial tamponade, secondary to disruption of coronary or epicardial vessels. More frequently the heart simply is contused like the bruise of a thigh muscle. This is shown on the tracing by an injury pattern.

A PHYSICIAN: *What happens to patients with tamponade treated with pericardiocentesis only?*

DR. EBERT: In many instances, these patients do well. However, the risk of operation in this group is negligible and in some of these patients a constrictive type pericarditis may develop later. I operated on one patient a month and a half after cardiac injury and there was a fibrous peel completely enveloping the heart. If one chooses not to operate, the patient should be followed closely for development of constrictive pericarditis or postpericardiotomy syndrome.

A PHYSICIAN: *What is postpericardiotomy syndrome?*

DR. EBERT: This has been a special interest of mine. It appears that all patients who have postpericardiotomy syndrome will react immunologically to a myocardial membrane portion antigen. They also react to the spun-down membrane layer of streptococcus. This raises the question of whether the syndrome is due to the development of autoimmunity or infection. If one follows patients with postpericardiotomy syndrome, the syndrome may be suppressed with steroids but not the antibody. One may also find the same antibody in patients following myocardial infarction and, for lack of a better term, we call this antiheart antibody. I therefore think that the syndrome is really not a pericardial problem but possibly has its source in the myocardium.

A PHYSICIAN: *What about a patient who arrives* in extremis?

DR. EBERT: It is much easier to recommend the type of treatment to be used for such patients than for those with less dramatic clinical symptoms. The indications for treatment are clear and time is of the essence. I immediately would carry out a left thoracotomy in the fourth intercostal space—extending it, if needed, by incising one or two costal cartilages near the left sternal border. The pericardium is then opened in a longitudinal fashion, avoiding injury to the phrenic nerve. The clot is simply scooped out and the bleeding point located. Once this is done, a finger may be inserted into the injury site to control hemorrhage and the patient quickly taken to the operating suite. Here repair can be undertaken with optimal lighting, exposure and assistance. This operation is well tolerated, particularly by young patients, and wound complications are surprisingly low.

A PHYSICIAN: *How can you be sure that you are dealing with pericardial tamponade?*

DR. EBERT: Usually the clinical situation is fairly clear. The patient is in shock, as manifested by poor peripheral perfusion. The sine qua non in shock from tamponade is distended neck veins. When distended neck veins and shock are present, one should also consider tension pneumothorax. Usually these two can be differentiated by feeling for the trachea and determining whether it is the midline. Ancillary signs include percussion tympany and decreased breath sounds on the side of the lesion. A tension pneumothorax can be quickly relieved by inserting a chest tube in the second intercostal space on the suspected side. If the patient is *in extremis* and tamponade is suspected, thoracotomy is clearly indicated and will lead to decompression of any tension pneumothorax that is present.

Refer to: Kan MK, Hopkins GB, Kristensen KAB, et al: Brain scintigraphy and intracranial neoplasms (Medical Information). West J Med 125:88-91, Jul 1976

Brain Scintigraphy and Intracranial Neoplasms

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SINCE BRAIN SCINTIGRAPHY was introduced more than 20 years ago it has become a well-established procedure in the diagnosis of neurological disorders. Its value in the diagnosis of intracranial neoplasms has been well-documented in several series carried out in large medical centers.[1-5] This report shows comparably good results in a 200 to 300 bed community hospital in a period of 11 years.

Methods and Materials

The case records of 73 patients in whom the diagnosis of brain tumors had been made were reviewed from the surgical and autopsy files for January 1964 through March 1975 in the Scripps Memorial Hospital. The cases of 69 patients in whom brain scintigrams were carried out within one month before surgical operation or autopsy were selected for the study. Two patients were excluded because the brain scintigrams were done 3 and 3½ months, respectively, before surgical operation. Two other patients were excluded because brain scans were not done until after operation. All patients except two were adults ranging from 19 to 70 years old. The two exceptions were an 11-year-old girl with dysgerminoma of the hypothalamus and a 12-year-old boy with Grade I astrocytoma of the left occipital area.

During the 11-year study period, a variety of radiopharmaceuticals and instruments were used. Of the 69 patients in the study, two patients received mercury-203 (Hg-203) chloromerodrin (750 microcuries) and five patients had mercury-197 (Hg-197) chloromerodrin (750 microcuries) in the early part of the study in 1964. These patients were scanned at 24 hours postinjection using a Nuclear-Chicago PhoDot scanner with 3 × 2 inch thallium activated sodium iodide crystal and a 19 hole collimator with a focal depth of 8 cm. The spectrometer was set at 260 to 300 kiloelectron volts (kev) for Hg-203 and 71 to 83 kev for Hg-197. Speeds for the scanner were 12 cm per minute for Hg-203 and 20 cm per minute for Hg-197 with a spacing of 4 mm. After 1964, technetium-99m (Tc-99m) in the form of pertechnetate or glucoheptonate was the radiopharmaceutical used for brain imaging. Sixty patients received 15 millicuries Tc-99m pertechnetate and the remaining two patients received 15 millicuries of Tc-99m glucoheptonate. Potassium perchlorate (800 mg) was given orally to the patients 15 minutes before the study in order to block the uptake by the choroid plexus, salivary gland and thyroid. Since the use of Tc-99m, the imaging instruments include a Searle Pho-Gamma III scintillation camera, a Searle Pho-Gamma III HP scintillation camera and a Nuclear Data Radicamera 60 scintillation camera. Cerebral flow studies were routinely carried out on the scintillation camera. High sensitivity collimators were used for the flow study with a 30 percent window while high resolution collimators were used for the static scintiphotos with a 20 percent window. Static scintiphotos with 350,000 counts were obtained at 1½ to 2 hours after injection of

TABLE 1.—*Sensitivity of Brain Scintigraphy by Tumor Size*

	No. of Cases	*Cases with Positive Scintigram*	*Sensitivity (percent)*
All cases	69	61	88.4
Larger than 2 cm	59	56	94.9
Equal to or less than 2 cm	10	5	50.0

TABLE 2.—*Sensitivity of Brain Scintigraphy by Location of Tumor*

	No. of Cases	*Cases with Positive Scintigram*	*Sensitivity (percent)*
All cases	69	61	88.4
Cerebrum	56	53	94.6
Pituitary fossa	4	2	50.0
Posterior fossa	9	6	66.7

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pertechnetate and ½ hour after glucoheptonate. All scintigrams were obtained in the anterior, posterior and both lateral positions. If necessary, delayed scintigrams were obtained at four to six hours postinjection.

Results

The brain scintigrams were abnormal in 61 of 69 patients, representing an overall sensitivity of 88.4 percent in our study.

The size and location of the tumors are the main factors affecting their detectability. For example, tumors of 2 cm or less in diameter were not diagnosed in 5 of 10 cases (50 percent) whereas only 3 of 59 cases (5.1 percent) of tumors greater than 2 cm in diameter were missed (Table 1). Deep seated tumors around the pituitary fossa are more difficult to detect by brain scan and two of four cases were not detected in our study (Table 2). A total of 26 metastatic intracranial neoplasms was present in our study. Two of four metastatic tumors in the cerebellum were missed and both of them were less than 2 cm in diameter. However, only one of 22 metastatic tumors in the cerebrum was not correctly diagnosed. The primary sites of the metastatic tumors were by majority the lung (15), followed by the breast (1), kidney (1), nasopharynx (1), melanoma (1), ovary (1), reticulum cell sarcoma (1) and lesions of unknown origin (5). The histological types of tumor and their overall detectability are summarized in Table 3. All high grade astrocytomas were diagnosed correctly whereas one of four low grade astrocytomas was missed. All gliomas of the cerebellum were correctly diagnosed whereas one of two acoustic neurilemmomas of 1.3 cm in diameter gave false negative findings on the brain scintigram. The single cases of colloid cyst, craniopharyngioma and cystic ependymoma all gave false negative results.

TABLE 3.—*Results of Brain Scans According to Histological Types*

Location and Histologic Type	*No. of Cases*	*Scan Findings*	
		Negative	*Positive*
Cerebrum			
Astrocytoma			
Grade I-II	4	1	3
Grade III-IV	16	0	16
Oligodendroglioma	1	0	1
Mixed glioma	1	0	1
Meningioma	9	0	9
Metastatic tumors	22	1	21
Ependymoma (cystic)	1	1	0
Undifferentiated tumor	2	0	2
Cerebellum			
Acoustic neurilemmoma	2	1	1
Metastatic tumor	4	2	2
Glioma	3	0	3
Pituitary fossa			
Chromophobe adenoma	1	0	1
Dysgerminoma	1	0	1
Craniopharyngioma	1	1	0
Colloid cyst	1	1	0

TABLE 4.—*Accuracy of Brain Scan in Proven Intracranial Tumors*

Authors	*Total No. of Cases*	*Cases with Positive Brain Scintigram*	*Sensitivity (percent)*
Goodrich et al (1965)	118	99	84.0
Overton et al (1965)	100	84	84.0
Witcofski et al (1967)	92	75	81.5
O'Mara and Mozley (1971)	88	73	83.0
Authors	69	61	88.4

Discussion

With the currently available instruments, our results in brain scintigraphy compare favorably with reports from large medical centers (Table 4). Our results indicate that size and location are important factors affecting the detection of brain tumors. Boller and co-authors[6] showed that brain tumors larger than 2.7 cm in diameter were missed by scintigraphy in only 3 percent of cases. As is the experience of others, we had very good results with high grade astrocytomas, supratentorial meningiomas and metastatic tumors in the cerebrum. Midline tumors around the pituitary fossa or lesions of 2 cm or less in diameter are not easily detected by the Anger scintillation camera. Tomographic data obtained with a rectilinear scanner or, better still, with a multiplane

TABLE 5.—*Neurodiagnostic Tests and Their Relative Percent Accuracy*

Authors	*Brain Scan*	*Skull Series*	*Echoencephalogram*	*Electroencephalogram*	*Arteriogram*	*Pneumoencephalogram and Ventriculography*
Goodrich et al	84.0	40.0	..	92.0	82.0	84.0
Overton et al	84.0	37.0	..	71.0	84.0	95.0
Witcofski et al	81.5	46.9	68.9	70.4	92.3	93.9
O'Mara and Mozley	83.0	..	..	..	86.5	95.4

tomographic scanner[7] may be expected with proper positioning to yield better results with midline tumors. Newer radiopharmaceuticals such as Tc-99m glucoheptonate and Tc-99m diethylenetriaminepentacetic acid (DTPA) are cleared rapidly from the blood stream and show little free pertechnetate concentration in mucosal areas. They would tend to improve the ability to detect abnormal concentrations of tracer near the base of the brain, particularly in the midline and in the posterior fossa.

The timing of brain scintigraphy after injection also affects the sensitivity of the procedure. Generally, delayed scintigraphy at three to four hours after injection of Tc-99m pertechnetate gives better results than early scans done within one hour after injection. Gates and co-authors[8] improved the detectability of brain tumors from 80 percent with routine early scintigraphy to 93 percent with delayed studies. Ramsey and Quinn[9] also confirmed the presence of increased visible abnormality in the delayed scintigrams in 39 of 74 patients with proven intracranial disease. Meisel and co-authors[10] suggest the use of delayed scintigraphy with 203 Hg-chlormerodrin at 24 hours after injection when delayed Tc-99m pertechnetate scintigrams are negative or equivocal in patients suspected of having lesions adjacent to the base of the skull, especially in the subtentorial region.

The greatest advantage of brain scintigraphy is its noninvasiveness. The overall accuracy of brain scintigraphy is about the same as cerebral arteriography,[4,11-13] which carries a significantly higher risk to the patient. Table 5 shows a comparison of the percent diagnostic accuracy of different neurodiagnostic tests. Unlike echogram or electroencephalogram, brain scan permits accurate and direct localization and visualization of the tumor, which is important to the neurosurgeon. The higher accuracy of pneumoencephalogram and ventriculography may represent an additive effect due to the use of brain scintigraphy as a screening test before performance of the air studies.[4] The successfulness of different procedures in brain tumor detection also depends on their location. While brain scintigraphy is very good in detecting superficial lesions, air contrast studies are better in deep-seated midline tumors.

The use of brain scintigraphy should not be considered as a competition to other radiological procedures but rather as a complement. For example Witcofski and co-authors[3] used brain scintigraphy to select the appropriate x-ray contrast study to improve the final diagnostic accuracy. While arteriography provides more precise information of the vascularization of the tumor, the direct visualization of lesions on the brain scintigram is often superior to the indirect evidence of displacement of vascular structures or air-filled spaces as in x-ray contrast studies.[4]

For the past 20 years brain scintigraphy has proved to be a useful tool in screening intracranial neoplasms. Newly available methods will, however, permit even a higher successful rate in the detection of brain tumors in the near future. Ostertag and co-authors[14] applied a dual isotope technique with scintigraphic and orthagonal multiple field digital measurements and succeeded in detecting more than 90 percent of basal supratentorial midline cerebral tumors and posterior fossa tumors. Kuhl and associates have developed a method of reconstructing a transaxial tomographic section of the head from a series of rectilinear scans carried out with scintillation detectors of conventional design.[15-17] Computerized axial tomography (CAT) with the EMI® scanner[18] (manufactured by EMI Medical, Inc., 3605 Woodhead Drive, Northbrook, IL 60062) is a revolutionary radiographic scanning technique that takes multiple x-ray transmission readings through the skull at one degree increments around the head. The linear x-ray attenuation coefficients of the brain tissues and cerebrospinal fluid are calculated on a computer and displayed pictorially as axial transverse layers of the head. Initial clinical trials[19-26] suggest that CAT provides a potentially powerful tool for the detection of intracranial neoplasms. The exact impact of CAT on radionuclide brain scintigraphy is still uncertain at present; however, the two procedures will likely be complementary to one another and in patients who cannot lie still or who are sensitive to iodinated contrast media, radionuclide brain scintigraphy would remain the procedure of choice.

The radiation dose from 15 millicuries of Tc-99m pertechnetate is approximately 0.16 rad to the whole body and 3 rads to the colon.[27] The small radiation dose permits brain scintigrams to be done in all age groups and to be repeated if necessary. Serial brain scintigrams are useful to assess the efficacy of various forms of therapy.

Summary

The diagnostic accuracy of brain scintigraphy in 69 histologically proven brain tumors was

studied in a 200 to 300 bed community hospital. The overall detectability of 88.4 percent favorably compares with results of several series carried out in large medical centers. The noninvasiveness and overall accuracy of brain imaging renders it a reliable procedure for screening patients with suspected intracranial neoplasms.

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Problems of Females Exposed to DES *In Utero*

Those female infants born to mothers who have received DES (diethylstilbestrol) are found to have a substantial probability of abnormalities of the cervix and vagina. I am cautious to say "abnormalities" of the cervix and vagina because they have *not* been found to have a very great likelihood of developing cancer. Indeed, in some large series of screening of patients whose mothers received DES, no case of vaginal or cervical cancer has been found. What has been found are lesions of the vagina and cervix which we call adenosis. On the other end of the scale, a very few patients have been seen with carcinoma of the vagina or cervix (clear-cell type). Essentially, all of these cases were products of a pregnancy that was exposed to DES. But that is not to say that many of the children who were so exposed will develop cancer, because most of them will not. It is important to explain that to the patient and to her parents. Her degree of risk of developing cancer is exceedingly slight, but it does exist.

—JAMES A. MERRILL, MD, *Oklahoma City*

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

AN HISTORICAL ACCOUNT OF PHARMACOLOGY TO THE 20TH CENTURY—Chauncey D. Leake, MD, Department of Pharmacology, University of California, San Francisco—A Publication in The Bannerstone Division of American Lectures in Pharmacology—Edited by Elton L. McCawley, MD, Department of Pharmacology, University of Oregon Medical School, Portland. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62717), 1975. 210 pages, $12.50 Cloth, $8.95 (Paperback).

In these fast moving times it is easy to forget that many of our most useful drugs (and poisons!) have their roots in antiquity. Dr. Leake's latest book is an excellent antidote for scientists with such lapses of memory. Consequently, even though the author considers his book "more appropriate for intelligent people generally than it is for professional pharmacologists or professional historians of medicine or science," it can be read with profit by anyone seriously interested in drug therapy. It is a rich source of information on prehistoric drug lore and the contents of early codifications of drugs and drug uses—it even tabulates the eight chief Egyptian medical papyri. More important, it traces the development of pharmacology through the long period of protopharmacology, and the transition to modern pharmacology around the close of the 18th century to the rapid, even explosive, development of pharmacology along with the other sciences in the 19th century. We are then left to contemplate the complex story of 20th century pharmacology and perhaps wonder how the labors and accomplishments of our times will look to future historians.

As always, Dr. Leake's easy style makes enjoyable reading—and history is better absorbed when administered in a palatable formulation. This book is not intended as the "definitive history of pharmacology," but it provides enough for most of us and a good takeoff point for anyone wishing to write the definitive history.

HENRY W. ELLIOTT, MD, PH D

* * *

STROKE AND ITS REHABILITATION—Volume 12 of Physical Medicine Library—Edited by Sidney Licht, MD, Curator, Physical Medicine Collections, Yale University Medical Library, New Haven; Associate Professor, Medical Library Science, University of Miami; With 16 contributors. Elizabeth Licht, Publisher, P.O. Box J, New Haven, CT (06515), 1975. 562 pages, $20.00.

This 12th volume of Dr. Licht's Physical Medicine Library again demonstrates his skills as an editor. He has attempted to collate pathology, diagnosis and medical and surgical management with the neurophysiological basis for rehabilitation of stroke victims into one comprehensive volume. Dr. Licht's expertise as a historian provides significant insight into the development of modern day management of hemiplegia.

An excellent chapter on the selection of wheelchairs for hemiplegic patients has been included which thoroughly discusses the accessories commonly available with specific indications as well as contraindications for their use. All too often the ambulatory capability of a stroke victim is impeded by inappropriate prescription of such assistive devices. One would like to see a more comprehensive discussion, perhaps even a separate section, on bracing of the lower extremity, including criteria for prescription as well as photographs of the devices frequently used in stroke rehabilitation.

One question that frequently arises in cerebrovascular accidents is how to select the patient who is a candidate for an aggressive, active rehabilitation program. A most thorough review, which should be considered essential reading for most medical specialists, is the chapter on rehabilitation potential by Dr. Jerome Gersten. It is perhaps the most comprehensive evaluation of documented prognostic factors that I have yet seen. Reference to this chapter could potentially decrease the costs of a rehabilitation program by more accurately selecting proper candidates. Excellent reviews are presented of physical therapy, occupational therapy in disorders of communication, and nursing care of stroke patients. The latter chapter should be required for all co-care programs for neurologic patients. The six clinical chapters provide good reviews, and of particular interest are the chapters on pharmacologic measures and surgical measures in stroke. The index is comprehensive and easy to use.

This book should have wide appeal as both a reference work and a clinical tome for residents and specialists dealing with cardiovascular disease, neurologic disorders and rehabilitation.

SHELDON BERROL, MD

* * *

GENERAL UROLOGY—Eighth Edition—Donald R. Smith, MD, Chairman and Professor, Division of Urology, University of California, San Francisco; Consulting Urologist, San Francisco General Hospital; Consulting Surgeon (Urology), Veterans Administration Hospital, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1975. 492 pages, $11.00.

Professor Donald R. Smith, of the University of California, San Francisco has "done it again," with the Eighth Edition of his already world-famous book, *General Urology*. He has once more given us the most complete, useful single volume paperback reference that there is in the urological textbook literature. He has brought us up-to-date from the excellent previous editions in English (which have been translated into German, Polish, Spanish and other languages).

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The paperback volume is lithographed and produced by Lange Medical Publications. It has a maximum amount of information about urology packed into a minimum of space. There may be some question about whether the chapter on "Impotence" is up-to-date; and there is an understandable personal bias concerning references to the literature from the various University of California medical faculties; for example, the section on "Renovascular Hypertension." The book is unusually well illustrated.

On the whole, the work is extremely useful and comprehensive. I tell our medical students it is a *must* for any student of urology.

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Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADVANCES IN MEDICAL COMPUTING—Proceedings of the Third International Symposium on Computers in Medicine—Edited by J. Rose, PhD, FRIC, MBIM, FIL, F InstCSc, MI EnvSc, College of Technology and Design, Blackburn; and J. H. Mitchell, MD(Glas), MRCP(Ed), MRCP(Glas), D Obst RCOG, M InstCSc, Consultant Physician, Paisley. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 189 pages, $29.50.

ANAESTHESIA FOR EYE, EAR, NOSE AND THROAT SURGERY—Edited by William F. K. Morrow, MB, FRCPE, FFARCSI, Consultant Anaesthetist, Royal Victoria Hospital, Belfast; and James D. Morrison, B Sc, MD, FFARCS, Consultant Anaesthetist, Royal Victoria Hospital, Belfast. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 149 pages, $17.50.

THE ARTERIES AND VEINS OF THE HUMAN SPINAL CORD FROM BIRTH—G. F. Dommisse, MD, ChM, FRCS(Ed), the Department of Orthopaedics, University of Pretoria, the Orthopaedic Hospital, the Department of Hospital Services, Transvaal Provincial Administration, Pretoria. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 104 pages, with illustrations, $29.50.

ATLAS OF MEDICAL HELMINTHOLOGY AND PROTOZOOLOGY—Second Edition—H. C. Jeffrey, CBE, MD, FRCPE, FRC Path, DTM & H, Major-General (Retd), National Medical Director, Scottish National Blood Transfusion Service; Formerly Director of Army Pathology and Consulting Pathologist to the Army; and R. M. Leach, BEM, The Royal Army Medical College, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 121 plates, $28.50.

BLOOD FLOW AND METABOLISM IN THE BRAIN—Proceedings of the 7th International Symposium on Cerebral Blood Flow and Metabolism—Edited by A. M. Harper, MD, Reader in Surgical Physiology, Wellcome Surgical Research Institute, and St. Mungo Department of Surgery, Glasgow Royal Infirmary; W. B. Jennett, MD, FRCS, Professor of Neurosurgery, Institute of Neurological Sciences, Glasgow; J. D. Miller, MD, PhD, FRCS, Senior Lecturer in Neurosurgery, Institute of Neurological Sciences, Glasgow; and J. O. Rowan, F Inst P, Principal Physicist, Institute of Neurological Sciences, and Department of Clinical Physics & Bio-engineering, Glasgow. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. $29.50.

CELL AND TISSUE CULTURE—Fifth Edition—John Paul, FRSE, MB, ChB, PhD, FRCP Ed, FRCP G, FRC Path, Director, Beatson Institute for Cancer Research, Glasgow. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 484 pages, $20.00.

CLINICAL IMPLICATIONS OF AIR POLLUTION RESEARCH—American Medical Association Air Pollution Medical Research Conference—Edited by Asher J. Finkel and Ward C. Duel. Publishing Sciences Group, Inc., 162 Great Road, Acton, MA (01720), 1976. 374 pages, $20.00.

CLINICAL PHARMACOLOGY—Second Edition—Paul Turner, MD, BSc, FRCP, Professor of Clinical Pharmacology, St. Bartholomew's Hospital, London; and Alan Richens, MB, PhD, MRCP, Senior Lecturer in Clinical Pharmacology, St. Bartholomew's Hospital, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th Street, New York City (10036), 1975. 256 pages, $7.50.

CLINICAL TOXICOLOGY OF COMMERCIAL PRODUCTS—Acute Poisoning—Fourth Edition: Robert E. Gosselin, MD, PhD, Irene Heinz Given Professor of Pharmacology, Dartmouth Medical School, Hanover, New Hampshire; Harold C. Hodge, PhD, DSc, Professor and Chairman Emeritus of Pharmacology and Toxicology, School of Medicine and Dentistry, The University of Rochester, Professor in Residence of Pharmacology and Oral Biology, University of California, San Francisco; of Environmental Toxicology, and of Pharmacology and Medical Therapeutics, University of California, Irvine; Roger P. Smith, PhD, Professor of Toxicology, Dartmouth Medical School; and Marion N. Gleason, MSc (hc), Honorary Associate, American Academy of Pediatrics, Formerly Research Associate in Pharmacology, School of Medicine and Dentistry, The University of Rochester, Rochester, New York. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1976. 1783 pages, $54.00.

CONTROVERSY IN CARDIOLOGY—The Practical Clinical Approach—Edited by Edward K. Chung, MD, Professor of Medicine, Jefferson Medical College of Thomas Jefferson University, and Director of the Heart Station, Thomas Jefferson University Hospital, Philadelphia. Springer-Verlag New York Inc., 175 Fifth Avenue, New York City (10010), 1976. 299 pages, with 99 figures, $29.80.

CONYBEARE'S TEXTBOOK OF MEDICINE—Sixteenth Edition—Edited by W. N. Mann, MD(Lond), FRCP, Physician to Guy's Hospital, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 887 pages, $45.00.

THE DEVELOPMENT OF THE INFANT AND YOUNG CHILD: Normal and Abnormal—Sixth Edition—R. S. Illingworth, MD LEEDS, FRCP, DPH, DCH, Professor of Child Health, The University of Sheffield; Paediatrician, the Children's Hospital and the Jessop Hospital for Women, Sheffield. Churchill Livingstone Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1975. 325 pages, $14.50.

DIET AWAY YOUR STRESS, TENSION, AND ANXIETY—The Fructose Diet Book—J. Daniel Palm, PhD, Associate Professor, St. Olaf College, Northfield, Minnesota. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 227 pages, $6.95.

DISEASES OF THE NOSE, THROAT AND EAR—A Handbook for Students and Practitioners: Eleventh Edition—I. Simson Hall, MB, ChB, FRCPEd, FRCSEd, Consulting Surgeon, the Royal Infirmary, Edinburgh, Lecturer Emeritus in Diseases of Nose, Throat and Ear, University of Edinburgh; and Bernard H. Colman, MA, BSc, ChM, FRCSEd, Senior Surgeon, Department of Otolaryngology, the Radcliffe Infirmary, Oxford, Clinical Lecturer in Otolaryngology, University of Oxford. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 352 pages, $12.50 (Softbound).

DRUG EFFECTS ON THE FETUS—A Survey of the Mechanisms and Effects of Drugs on Embryogenesis and Fetogenesis—Monographs on Drugs—Volume 2: Series Editor: Graeme S. Avery, MPS, Auckland, New Zealand. H. Tuchmann-Duplessis, Laboratoire d'Embryologie, Faculte de Medecine de Paris et Biologiste des Hopitaux de Paris-Chef de Services. Publishing Sciences Group, Inc., 162 Great Road, Acton, MA (01720), 1975. 267 pages, $15.00.

EXERCISES IN NEUROLOGICAL DIAGNOSIS—Second Edition—John H. Tyrer, MD(Sydney), FRCP(Lond), FRCP(Edin), FRACP, Professor of Medicine, University of Queensland; Senior Neurologist, Royal Brisbane Hospital; Honorary Consulting Physician, Mater Misericordiae Hospital, Brisbane; and John M. Sutherland, MD(Glasgow), FRCP(Edin), FRACP, Senior Neurologist, Royal Brisbane Hospital and Royal Brisbane Children's Hospital; Honorary Reader in Neurology, University of Queensland. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 311 pages, $17.50.

THE FATHERHOOD FORMULA—Jerome Burton, MD, and Milt Rosen, MS. Major Books, 21322 Lassen St., Chatsworth, CA (91311), 1976. 180 pages, $1.50 (Paperback).

FOREIGN TRAVEL IMMUNIZATION GUIDE—Fifth Edition—Hans H. Neumann, MD, Director of Preventive Medicine, Department of Health, New Haven, Connecticut. H. H. Neuman, MD, P.O. Box 611, New Haven, CT (06503), 1976. 32 pages, $2.50 (Paperback).

FUNDAMENTALS OF ABDOMINAL AND PELVIC ULTRASONOGRAPHY—Volume 6 in the Series: Saunders Monographs in Clinical Radiology. George R. Leopold, MD, Associate Professor of Radiology; Head, Division of Ultrasound, University of California, San Diego, School of Medicine; and W Michael Asher, MD, & Cdr, MC USN, Head, Division of Ultrasound, Naval Regional Medical Center, San Diego; Clinical Assistant Professor of Radiology, University of California, San Diego, School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 267 pages, with 254 illustrations, $21.50.

GENERAL PRACTICE MEDICINE—Edited by J. H. Barber, MD, MRCGP, D Obst, RCOG, Professor of General Practice, Norie-Miller Chair, University of Glasgow; and F. A. Boddy, MB, ChB, MFCM, DPH, Senior Lecturer, Department of Community Medicine, University of Glasgow; Foreword by E. V. Kuenssberg, CBE, MB, ChB, FRCGP, Formerly Chairman of the Scottish General Medical Services Committee, 1962-66, and of the Council of the Royal College of General Practitioners, 1971-74. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 352 pages, $16.50 (softbound).

GYNAECOLOGICAL MALIGNANCY—Clinical and Experimental Studies—Edited by M. G. Brush, PhD, Senior Lecturer in Biochemistry, Department of Gynaecology, St. Thomas's Hospital Medical School, London; and R. W. Taylor, MD, FRCOG, Professor of Gynaecology, St. Thomas's Hospital Medical School. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1975. 274 pages, $24.75.

GYNAECOLOGICAL PATHOLOGY—Second Edition—Magnus Haines, MD (Lond), FRCOG, FRC Path, Consultant Pathologist, Director of Department of Pathology, Chelsea Hospital for Women, Institute of Obstetrics and Gynaecology, University of London; Consultant Pathologist and Honorary Curator, Royal College of Obstetricians and Gynaecologists; and Claud W. Taylor, MB, ChB(Birm), FRCOG, FRC Path, Late Senior Research Fellow, Department of Pathology, The Medical School of Birmingham; Formerly Consultant Pathologist, Director of Department of Pathology, the Birmingham and Midland Hospitals for Women, United Birmingham Hospitals. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 552 pages, $40.00.

HANDBOOK OF ORTHOPTIC PRINCIPLES—Third Edition—G. T. Willoughby Cashell, MB, BS Lond, FRCS Ed, FRCS Eng, Emeritus Consultant, Ophthalmic Surgeon, Royal Berkshire Hospital, Reading; and Isobel M. Durran, DBOT, Formerly Orthoptist-in-Charge, School of Orthoptics, Oxford Eye Hospital. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1974. 137 pages, $8.00 (softbound).

HEALTH CARE DELIVERY SYSTEMS—Evaluation Criteria—J. W. Lapatra, PhD, Associate Professor, Department of Community Health, University of California, Davis, School of Medicine. Charles C Thomas, Publisher, 301-327 Lawrence Avenue, Springfield, IL (62703), 1975. 358 pages, $21.50.

HUMAN NEUROANATOMY (Formery Strong and Elwyn's Human Neuroanatomy)—Seventh Edition—Malcolm B. Carpenter, MD, Professor of Anatomy, College of Physicians and Surgeons, Columbia University. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1976. 741 pages, $25.00.

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1—**The Chest.** 86 pp. 172 figs. $4.95. 1970. **Order #8525-4.**
2—**The Abdomen.** 88 pp. 122 figs. $4.95. 1971. **Order #8526-9.**
3—**Bone.** 85 pp. 138 figs. $4.95. 1972. **Order #8527-7.**
4—**The Total Patient.** 139 pp. 173 figs. $5.95. 1972. **Order #8528-5.**
5—**Pediatrics.** 162 pp. 239 figs. $6.95. 1973. **Order #4630-1.**
6—**Nuclear Radiology.** 218 pp. 261 figs. $6.95. 1973. **Order #5103-8.**
7—**The Emergency Patient.** 240 pp. 158 figs. $7.95. 1975. **Order #5627-7.**

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(Continued from Page 26)

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COLLEGE HEALTH PHYSICIAN—12-month position. Generalist or Internist. 60 miles north of San Francisco to join a four-doctor outpatient clinic. No nights or weekends. Salary competitive. Send résumé and curriculum vitae by August 1, 1976 to Personnel Office, Room 1012, Stevenson Hall, California State College, Sonoma, Rohnert Park, CA 94928. Equal Opportunity—Affirmative Action—Title IX Employer.

ORTHOPEDIST—364-bed GM&S Hosp. Malpractice liability protection. Liberal salary, vacation, retirement, and other benefits. Beautiful recreational area. U.S. Citizenship desirable. Licensure in any state is acceptable. Call collect to E. R. Cleveland, MD, Chief of Staff, Veterans Administration Hospital, Roseburg, Oregon 97470. Tele. (503) 672-4411 ext. 287. An equal opportunity employer.

FACULTY FOR EMERGENCY MEDICINE RESIDENCY PROGRAM beginning July 1976, university affiliated teaching hospital. Board Certified in Surgery, Internal Medicine or recent graduate-approved residency in Emergency Medicine. Salary competitive; malpractice insurance paid. California license necessary. Send curriculum vitae and names of three references to: William G. Malette, MD, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305. Telephone: (805) 323-7651, extension 346.

RESIDENCY IN EMERGENCY MEDICINE beginning July 1976. Two-year program, prerequisite one year post-graduate training. Busy Emergency Department in university affiliated teaching hospital. Send résumé and three letters of recommendation (or names of three references) to: William G. Malette, MD, Kern Medical Center, 1830 Flower St., Bakersfield, CA 93305. Telephone: (805) 323-7651, extension 346.

ORTHOPEDIC SURGEON (ACADEMIC), to establish a teaching service in a university affiliated VA Hospital. Board certification in orthopedic surgery necessary. Send curriculum vitae and references to Veterans Administration Hospital; 510 E. Stoner; Shreveport, LA 71130.

PRIMARY CARE PHYSICIANS—If you are interested in living in the Pacific Northwest, we may be able to assist you in finding the practice location best suited to your professional and personal interests in Washington State. The Clearinghouse: Community Advocates for Health Resource Development, a non-profit organization, works in collaboration with the Washington State Medical Association. Write for complete information. 1370 Stewart St., Seattle, Wash. 98109. Phone (206) 624-3272.

DIAGNOSTIC RADIOLOGIST—Board Certified/Eligible, to join as third man in Department of 48 man multispecialty group. Beautiful coastal area. W. Richard Ellis, Administrator, P.O. Drawer LL, Santa Barbara, CA 93102.

PHYSICIANS WANTED—Well established Medical Community badly needs three Family Practitioners, Two Ophthalmologists, one Dermatologist, one Urologist, and two Pediatricians. Opportunity to set up independent practice in a Medical Community with long established overflow practices. Guaranteed income, Rent Assistance, and generous financing for equipment available. Write: Charles Correll, P.O. Box 7011, Houston, Texas 77008; include curriculum vitae and photo.

PHYSICIAN

G.P. or F.P. to join the Texas Department of Corrections at Huntsville, Texas. Texas license required. Salary $34,300 per year. Malpractice insurance provided by the state. Other considerations include housing, utilities, food, and dry cleaning. Fringe benefits available. Apply to **Ralph E. Gray, MD, Texas Department of Corrections, P.O. Box 32, Huntsville, Texas 77340, or phone (713) 295-6371.**

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REASONABLE MALPRACTICE is still available in Colorado. GP or FP physician needed for rural community. Clinic provided adjacent to well equipped modern hospital. We are in urgent need, so willing to discuss any type of arrangement. Contact Gary Thompson, Southeast Colorado Hospital, Springfield, Colorado 81073. Phone (303) 523-4501.

MULTI-SPECIALTY GROUP on San Francisco Peninsula has opening for General Internist starting July 1976; salary negotiable, flexible call schedule, corporate benefits. Phone or write: James E. Lewis, MD, Sunnyvale Medical Clinic, Inc., 596 S. Carroll St., Sunnyvale, CA 94086; (408) 739-0551.

ASSISTANT/ASSOCIATE PROFESSOR OF ORTHOPAEDICS—The School of Medicine of the University of California, Davis, invites applicants for an Assistant/Associate Professor for Fall, 1976. This position requires a Board Eligible or Board Certified orthopaedist with demonstrated teaching and research abilities with training and experience in trauma, children's orthopaedics, and adult reconstructive surgery. Applicants should send a curriculum vitae by August 1, 1976, to: Paul R. Lipscomb, MD, Chairman, Department of Orthopaedics, University of California, Davis, Professional Building, Room 212, 4301 "X" Street, Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

WHIDBEY ISLAND, NORTHWEST WASHINGTON, needs two family physicians. Rural setting, 90 min. from Seattle. Active affiliation with University of Washington Family Medicine teaching program. 44 bed modern, well-equipped hospital. Offices, equipment available. Excellent recreational opportunities. Bob Zylstra, Administrator, Whidbey General Hospital, P.O. Box 400, Coupeville, WA 98239, (206) 678-5151.

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OTOLARYNGOLOGY—Seek partner for solo very active private practice in Southern California. Outside of Los Angeles basin to avoid attendant city problems yet close enough to utilize its facilities: John J. Manning, MD, 44804 N. Elm Ave., Lancaster, CA 93534; (805) 948-4528.

ASSISTANT PROFESSOR OF ORTHOPAEDICS—The School of Medicine of the University of California, Davis, invites applicants for an Assistant Professor for Fall, 1976. This position requires a Board Eligible or Board Certified orthopaedist with demonstrated teaching and research abilities with training and experience in trauma, arthritis, and joint reconstruction. Applicants should send a curriculum vitae by August 1, 1976, to: Paul R. Lipscomb, MD, Chairman, Department of Orthopaedics, University of California, Davis, Professional Building, Room 212, 4301 "X" Street, Sacramento, CA 95817. The University of California is an Affirmative Action/Equal Opportunity Employer.

PHYSICIAN—Full time and part-time openings in an innovative total community health program. Unique opportunity to become involved in clinical, public and rural health activities. Public health interest, experience, training desirable. California license required and Spanish fluency would be valuable. Contract range $37,000 to $42,000. Contact Donald T. Rice, MD, P.O. Box 11867, Fresno, CA 93775 or call (209) 488-3953.

PHYSICIAN—Full-time opening in the Narcotic Abuse Treatment Program. Would be giving examinations and working with illnesses related to the use of narcotics. Involves working with teams in two clinics. California license required, community education experience would be valuable. Contract range $37,000-$40,950. Contact George Wilson, Department of Health, P.O. Box 11867, Fresno, California 93775, or call (209) 488-3055.

PRIMARY CARE PHYSICIAN, CALIFORNIA, eligibility or certification for family practice preferred, must have one year residency training; for young primary-care multispecialty group, greater Los Angeles area, clinic-hospital operations, excellent salary ($4,500-6,000+ per month), fringes, no overhead, challenging opportunity; immediate placement; send résumé to Barbara, Spectro Health Services, 450 N. Roxbury Drive, Beverly Hills, CA 90210.

(Continued on Page 30)

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(Continued from Page 28)

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INTERNIST: Board Certified Internist wanted to associate with established physician and surgeon; new office facilities in a community with a 60,000 population service area, and excellent outdoor recreation. Please call or write: Alan E. King, MD, 1122 N.W. Garden Valley Blvd., Roseburg, Oregon 97470.

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MICRONESIA—The Trust Territory Government has openings for physicians to serve in the islands of Micronesia. These are two year, contract assignments with family transportation and housing provided. Please send résumé or request applications from Trust Territory Liaison Office, Bldg 112, Fort Mason, San Francisco, California 94123 (415) 561-5854

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RADIOLOGIST—Board certified, married, University trained. Special procedures performed. Ultrasound, Nuclear Medicine, Radiotherapy, available immediately. Will do locum tenens. California licensed. Phone (714) 894-5051. 8192 Ingram Circle, Westminster, CA 92683.

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CANCER

October 6—**Urological Cancer Conference—4th Annual.** Los Angeles Urological Society and American Cancer Society, California Division, at Century Plaza Hotel, Los Angeles. Monday. Contact: William Tanner, L.A. Cancer Society, 2932 Wilshire Blvd., Santa Monica 90403. (213) 828-7474.

October 29-30—**The Professional Team Approach to Cancer Health Care.** Claire Zellerbach Saroni Tumor Institute, Mt. Zion Hospital and Medical Center, at Hyatt Regency, San Francisco. Friday-Saturday. 11½ hrs. $110 for team (physician and one supportive professional); $85 for physician. Contact: Dept. of Continuing Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

MEDICINE

August 3—**Seminars in Nephrology.** USC. Tuesday.

August 25-27—**Cardiology Today: For the Physician in Clinical Practice.** Mt. Zion Hospital and Medical Center, Univ. of Pittsburgh School of Medicine, under auspices of the Council on Clinical Cardiology of American Heart Assn., at St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Cont. Education, Mt. Zion Hospital & Medical Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

September 9-11—**Dermatology for the Family Physician and Internist.** Memorial Hospital Medical Center of Long Beach at Del Webb's Newporter Inn, Newport Beach. Thursday-Saturday. 21 hrs. $150 for physicians; $100, residents and interns. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

September 11—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday. $70

September 12-16—**American Academy for Cerebral Palsy.** Century Plaza Hotel, Los Angeles. Sunday-Thursday. 18 hrs. $85. Contact: James Bryan, Exec. Sec., AACP, 1255 New Hampshire Ave. NW, Suite 1030, Washington, D.C. 20036. (202) 659-8251.

September 13-17—**Dermatology for Primary Care Physicians.** UCSF. Monday-Friday. $400. Intensive preceptorial course presenting practical management of skin diseases that constitute a large part of daily practice. Enrollment limited to 10 primary care providers.

September 15-17—**Clinical Allergy for the Office Practitioner—International Symposium.** PMC at Rickey's Hyatt House, Palo Alto. Wednesday-Friday. $25.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. 11½ hrs. Contact: Ann Raisbeck, Dept. of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

September 18-19—**Practical Gastroenterology for the Family Physician.** UCLA. Saturday-Sunday.

September 21—**Lyman A. Brewer, III, Cardiothoracic Symposium—2nd Annual.** White Memorial Medical Center at Hilton Hotel, Los Angeles. Tuesday. Contact: Howard Whigham, White Memorial Medical Center, 1720 Brooklyn Ave., Los Angeles 90033. (213) 269-9131, ext. 429.

September 29-30—**American Heart Association, Greater Los Angeles Affiliate—44th Annual Fall Symposium and 9th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday; 12 hrs. $60 for member of any heart assn.; $80, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 29-October 1—**San Francisco Heart Association—46th Annual Symposium.** Masonic Auditorium, San Francisco. Wednesday-Friday. Contact: S.F. Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

October 1-2—**Clinical Allergy.** Children's Hospital Medical Center, Oakland, at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Carty Calori, Med. Staff Admin. Asst., Children's Hospital Medical Center, 51st and Dover Sts., Oakland 94609. (415) 654-5600.

October 2-3—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 8-9—**Techniques for Dermatologic Research in the Office.** UCSF. Friday-Saturday.

October 12-14—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Golden Gateway Holiday Inn, San Francisco. Tuesday-Thursday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

October 14-17—**California Society of Internal Medicine—Annual Meeting.** Del Monte Hyatt, Monterey. Thursday-Sunday. Contact: Carol Holland Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 16-17—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 16-17—**Dermatologic Surgery.** See Surgery, October 16-17.

October 18-22—**Workshops in Internal Medicine.** American College of Physicians at University of Hawaii, Honolulu. Monday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, Pa. 19104.

OBSTETRICS AND GYNECOLOGY

July 17-19—**Basic Laparoscopy: Current Principles and Practice.** UCSD at Sea Lodge, La Jolla. Saturday-Monday.

September 9-12—**Neonatology.** UCSD at Town and Country Convention Center, San Diego. Thursday-Sunday. Contact: Louis Gluck, MD, C-019 Biology Bldg., UCSD. (714) 452-4424.

September 13-15—**Medical Complications in Obstetrics and Gynecology—Annual Fall Symposium.** UCSF at Hyatt on Union Square, San Francisco. Monday-Wednesday.

September 16-18—**Workshops in (1) High Risk Pregnancy and (2) Infertility.** UCSF at Royal Lahaina Hotel, Maui, Hawaii. Thursday-Saturday.

October 1-3—**Symposium on Perinatal Medicine.** National Foundation/March of Dimes; Long Beach and Orange County Obstetrics-Gynecology Societies; UCI at Memorial Hospital Medical Center, Long Beach. Friday-Sunday. $150. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3823.

October 2—**Endometriosis: Current Principles and Management—16th Annual Fall Seminar in Obstetrics and Gynecology.** Shufelt Society of Santa Clara Valley at Le Baron Hotel, San Jose. Saturday. 7 hrs. Contact: Vincent F. Nola, MD, Sect., Shufelt Society, 2081 Forest Ave., San Jose 95128.

October 6-8—**Recent Trends in Ob-Gyn.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

October 25-26—**New Horizons in Perinatal Intensive Care—5th Annual Seminar.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. Contact: Robin J. Grant, MPH, Coord. of Cont. Ed., Harbor General Hospital, 1124 W. Carson, Torrance 90502. (213) 328-2380, ext. 1374.

October 29—**Advances in Obstetrics and Gynecology.** UCD and Northern California Ob-Gyn Society at Red Lion Motor Inn, Sacramento. Friday. Contact: UCD.

PEDIATRICS

September 12-16—**American Academy for Cerebral Palsy.** See Of Interest to All, September 12-16.

September 22-23—**Brennemann Memorial Lectures—33rd Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Gene Black, LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

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RADIOLOGY AND PATHOLOGY

August 1-7—**American Institute of Ultrasound in Medicine.** Hyatt Regency, San Francisco. One week. Contact: Ms. D. LaMaster, Exec. Sec., P.O. Box 25606, Oklahoma City 73125.

September 18—**Radiology Symposium.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 1-3—**Society of Nuclear Medicine—1st Annual Western Regional Meeting.** Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Justine J. Lynch, Exec. Sec., No. and So. Calif. and Pacific NW Chapters, SNM, P.O. Box 40279, San Francisco 94140.

October 15-17—**Radiology of the Genitourinary System.** American College of Radiology at Fairmont Hotel, San Francisco. Friday-Sunday. 15 hrs. $200 for members; $240, nonmembers. Contact: Maurine H. Trautz, Conf. Coord., ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015. (301) 654-6900.

October 21-29—**American Society of Clinical Pathologists and College of American Pathologists.** Hilton Hotel, Los Angeles. Nine days. Contact: D. L. Gilcrest, ASCP, 2100 W. Harrison St., Chicago 60612.

October 26-29—**Symposium in Diagnostic Radiology.** UCSD at Vacation Village, San Diego. Tuesday-Friday.

SURGERY AND ANESTHESIOLOGY

July 15-16—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 1-8—**International College of Surgeons—3rd Annual Hawaii Meeting.** Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $100. Contact: William A. Houser, Admin. Dir., ICS, 1516 N. Lake Shore Dr., Chicago 60610. (312) 642-3555, ext. 61.

August 1-13—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1,200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

August 5-6—**Keratoplasty.** PMC at Stanford Court Hotel, San Francisco. Thursday-Friday. $175.

August 6-7—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hospital Medical Center, 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

August 7-14—**Diagnosis and Management of Corneal and External Disease Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 12-13—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

August 15-18—**Urology.** UCLA at Lake Arrowhead. Sunday-Wednesday.

September 10-11—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

September 11-18—**Practical Management of Anesthetic Problems—2nd Annual Symposium.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 12-16—**American Academy for Cerebral Palsy.** See Of Interest to All, September 12-16.

September 15-16—**Strabismus.** PMC at Stanford Court Hotel, San Francisco. Wednesday-Thursday. $175.

September 16-17—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 9-13—**American Society of Anesthesiologists—Annual Meeting.** Hilton Hotel, San Francisco. Saturday-Wednesday. 45 hrs. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

October 10-22—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 11-12—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Monday-Tuesday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

October 14-15—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 16-17—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

August 2-6—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

August 14-25—**Postgraduate Refresher Course—19th Annual.** USC, Univ. of Hawaii School of Medicine, Tripler General Hospital at Honolulu and Maui or Kauai, Hawaii. 12 days.

August 18-22—**Family Practice Refresher Course—3rd Annual.** UCLA. Wednesday-Sunday.

August 22-27—**Family Practice Refresher Course.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

August 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD. Monday-Friday.

August 28-September 4—**Family Practice Refresher Course—7th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $225. Contact: J. Blair Pace, MD, 101 City Dr. So., Orange 92668. (714) 634-5171.

August 29-September 2—**Autogenic Training.** UCLA at Asilomar. Sunday-Thursday.

August 29-September 6—**Pharmacology.** UCSF at Maui, Hawaii. Nine days.

August 31-October 19—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 9-11—**Dermatology for the Family Physician and Internist.** See Medicine, September 9-11.

September 12-16—**American Academy for Cerebral Palsy.** Century Plaza Hotel, Los Angeles. Sunday-Thursday. 18 hrs. $85. Contact: James Bryan, Exec. Sec., AACP, 1255 New Hampshire Ave. NW, Suite 1030, Washington, D.C. 20036. (202) 659-8251.

September 13-17—**Dermatology for Primary Care Physicians.** See Medicine, September 13-17.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** See Medicine, September 17-18.

September 18-19—**Practical Gastroenterology for the Family Physician.** See Medicine, September 18-19.

September 20-24—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

September 20-24—**Topics in Emergency Medicine—Basic Course.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

October 7-9—**Western Occupational Health Conference—20th Annual.** Western Occupational Medical Association at Marriott Hotel, Los Angeles. Thursday-Saturday. Contact: Jack Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 11-15—**Primary Care.** STAN. Monday-Friday. $250.

October 21-22—**Geriatrics.** UCSF at Veteran's Home of California, Napa. Thursday-Friday.

October 24-27—**California Academy of Family Physicians.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: William R. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

October 25-29—**Family Practice Review.** LLU. Monday-Friday.

October 25-29—**Global Medicine and Diseases of Travel—120th Annual Scientific Meeting.** Hawaii Medical Association at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., HMA, 510 S. Beretania St., Room 201, Honolulu 96813. (808) 536-7702.

October 30-31—**Physiology of Respiration.** UCSF. Saturday-Sunday.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

August 4-6—**Woodland Park Hospital Family Practice Symposium on Immunology.** Gearhart by the Sea, Gearhart, Oregon. Contact: R. T. Gustafson, MD, Woodland Park Hospital, Department of Family Practice, 10300 N.E. Hancock Street, Portland 97220.

SURGERY

September 6-7—**Western Orthopedic Society Annual Meeting.** Sunriver Lodge, Bend. Contact: Stanley E. Donahoo, MD, 1819 West Harvard Blvd., Roseburg 97470.

OF INTEREST TO ALL PHYSICIANS

August 20-21—**John Tomlin Memorial Cancer Lectures,** Rogue Valley Country Club, Medford. Contact: June Peters Byers, MD, 907 E. Main, Medford, 97501.

September 22-24—**Oregon Medical Association Annual Scientific Session.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

July 26-29—**World of the Heart and Lung: America's Hearts and Lungs After 200 Years.** Monday-Thursday. University Tower Hotel, Seattle. 24½ hrs. $155. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

August 3-6—**American Academy of Clinical Toxicology and American Association of Poison Control Centers Joint Meeting.** Tuesday-Friday. Olympic Hotel, Seattle. Hours to be determined. Members, $50; non-members, $75; interns, residents, allied health personnel, $10. Contact: Barry H. Rumack, MD, Rocky Mountain Poison Control Center, West 8th and Cherokee St., Denver, CO 80204.

September 10-11—**University of Washington School of Medicine Alumni Days.** Friday-Saturday. Univ. of Wash. Sch. of Med., Seattle. Contact: John N. Lein, MD, Dir. CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 10-13—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan R. Knudson, Exec. Dir., 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110 or 1-800-552-0602.

September 13-17—**University of Washington School of Medicine Montana Circuit Course on Cancer.** Kalispell, Havre, Butte, Miles City. Dates and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 17—**Practical Aspects of Clinical Anaerobic Microbiology.** Friday. Location, hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 17-18—**Medical Genetics.** Friday-Saturday. Child Development and Mental Retardation Center, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

September 23-24—**Ophthalmology and Otolaryngology for Primary Physicians.** Thursday-Friday. Seattle. Location, hours and fee to be determined. Contact: Div. of CME, HSC SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

October 1-2—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 6—**Internal Medicine Review Sessions.** Wednesday evenings to June 1. Univ. of Wash. Sch. of Med., Seattle. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

October 6-8—**Clinical Topics in Chest Disease.** (ACP). Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 19½ hrs. Fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 7-8—**Hospital and Health Facilities Infectious Disease Control.** Thursday-Friday. Seattle. Location, hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

October 7-9—**West Coast Allergy Society Annual Scientific Program.** Thursday-Saturday. Washington Plaza Hotel, Seattle. Contact: William H. Wilson, MD, Program Chairman, West Coast Allergy Society, 2164 S.W. Park Place, Portland, OR 97205. (503) 226-1555.

October 11-15—**University of Washington School of Medicine Eastern Washington Circuit Course on Pain.** 11, Moscow, ID; 12, Walla Walla; 13, Tri-Cities; 14, Yakima; 15, Wenatchee. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

October 22-23—**Aging and the Elderly.** Friday-Saturday. Seattle. Location, hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

October 22-23—**Sports Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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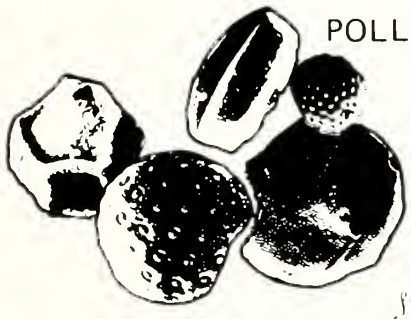

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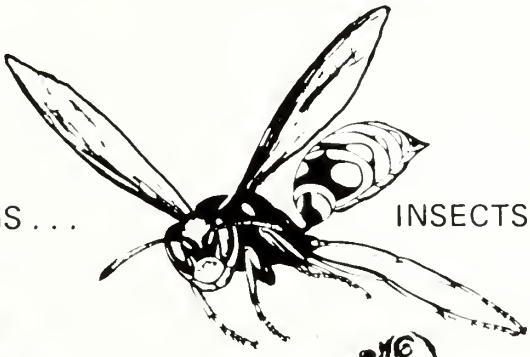

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REFERENCES

M. Ceska, R. Eriksson, and J.M. Varga
Radioimunosorbent Assay of Allergens –
The Journal of Allergy and Clinical Immunology
Vol. 49, No. 1-9, 1972

Wide L. et. al
Diagnosis of Allergy by an In Vitro Test for Allergen Antibodies
Lancet 2:1105, 1967

A. F. Lopapa, W.R. MacLaren
An In Vitro Test as used in the detection of immediate hypersensitivity in man.
V Latin American Congress of Allergy and Immunology National Academy of Medicine
Buenos Aires, Argentina, October 1974

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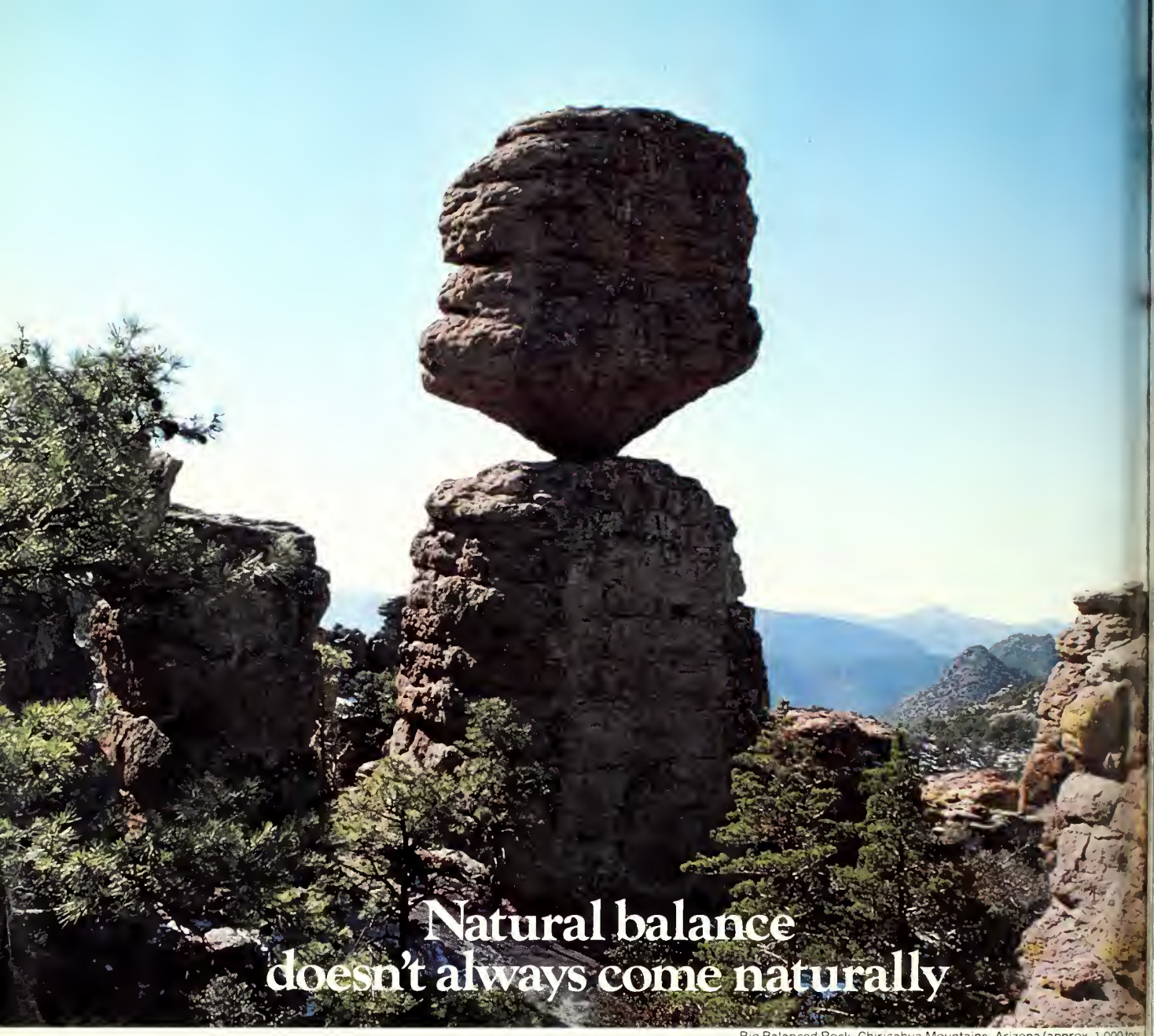
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■ **Dosage for Vertigo***—The usual adult dosage for Antivert/25 is one tablet t.i.d.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done, therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy. See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

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The ultimate objective test sleep laboratory proof of effectiveness ... now in geriatric insomnia patients

Six female insomniacs, ranging in age from 67 to 82 yea received Dalmane (flurazepam HCl) for seven consecuti nights in the sleep research laboratory.[1] Improvement over p treatment baseline levels was significant for sleep induction a sleep maintenance ($p<.05$). And the greater the sleep proble in these patients, the better the effect with Dalma (significant correlation at $p<.01$ lev

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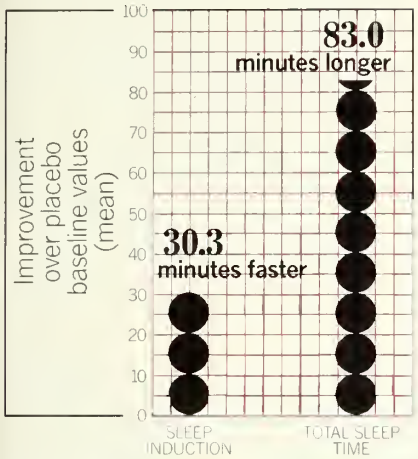
Elderly insomniacs fell asleep faster, slept longer[1]



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Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES:

1. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
3. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641

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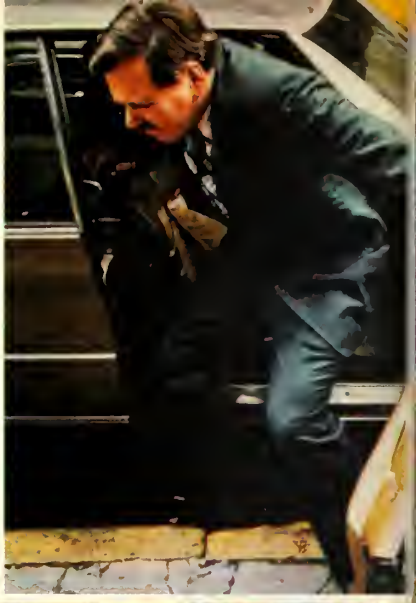

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Contraindications: Acute intermittent porphyria and allergic or idiosyncratic reactions to carisoprodol or related compounds such as meprobamate, mebutamate, tybamate.
Warnings: *Idiosyncratic Reactions:* Rarely, extreme weakness, transient quadriplegia, dizziness, ataxia, temporary vision loss, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation have appeared within minutes or hours of the first dose. These usually subside in several hours but supportive and symptomatic therapy, including hospitalization, may be necessary.
Pregnancy and Lactation. Safe use not established; weigh potential benefits against potential hazards in pregnancy, nursing mothers (concentrations in breast milk are two to four times that in plasma), or women of childbearing potential.
Children Under Twelve: Not recommended.
Potentially Hazardous Tasks: Driving a motor vehicle or operating machinery.
Additive Effects: Effects of carisoprodol and alcohol, other CNS depressants or psychotropic drugs may be additive.
Drug Dependence: Use cautiously in addiction-prone patients.
Precautions: To avoid excess accumulation, use caution in patients with compromised liver or kidney function.
Adverse Reactions: *Central Nervous System.* Drowsiness, dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, idiosyncratic reaction (see "Warnings").
Allergic or Idiosyncratic: In previously unexposed patients, these are usually seen after 1-4 doses and include rash, erythema multiforme, pruritus, eosinophilia, fixed drug eruption with cross reaction to meprobamate. Asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock may be manifestations of severe reactions. In such cases, stop carisoprodol and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids).
Cardiovascular: Tachycardia, postural hypotension, facial flushing.
Gastrointestinal: Nausea, vomiting, hiccup, epigastric distress.
Hematologic: Leukopenia and pancytopenia (on carisoprodol plus other drugs).
Usual Adult Dosage: One 350 mg tablet three times daily and at bedtime.
Overdosage: Has produced stupor, coma, shock, respiratory depression, and, very rarely, death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, treat symptomatically; cautiously give respiratory assistance, CNS stimulants, pressor agents as needed. Carisoprodol is metabolized in the liver and excreted by the kidney. Diuresis and dialysis have been used successfully with related drug meprobamate. Carefully monitor urinary output; avoid overhydration; observe for possible relapse due to incomplete gastric emptying and delayed absorption.
Before prescribing, consult package circular or latest PDR information.

1. Hindle, T.H. III: Calif. Med. 117:7 (Aug.) 1972. 2,3. Unpublished Data on file, Medical Department, Wallace Laboratories, Cranbury, N.J.

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If he's making the rounds of San Francisco...

Antivert®/25
(meclizine HCl) 25 mg. Tablets
for vertigo*

▪ **Most Widely Prescribed**—Antivert is the most widely prescribed agent for the management of vertigo* associated with diseases affecting the vestibular system such as Menière's disease, labyrinthitis, and vestibular neuronitis.

▪ **Relief of Nausea and Vomiting**—Antivert/25 can relieve the nausea and vomiting often associated with vertigo.*

▪ **Dosage for Vertigo***—The usual adult dosage for Antivert/25 is one tablet t.i.d.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

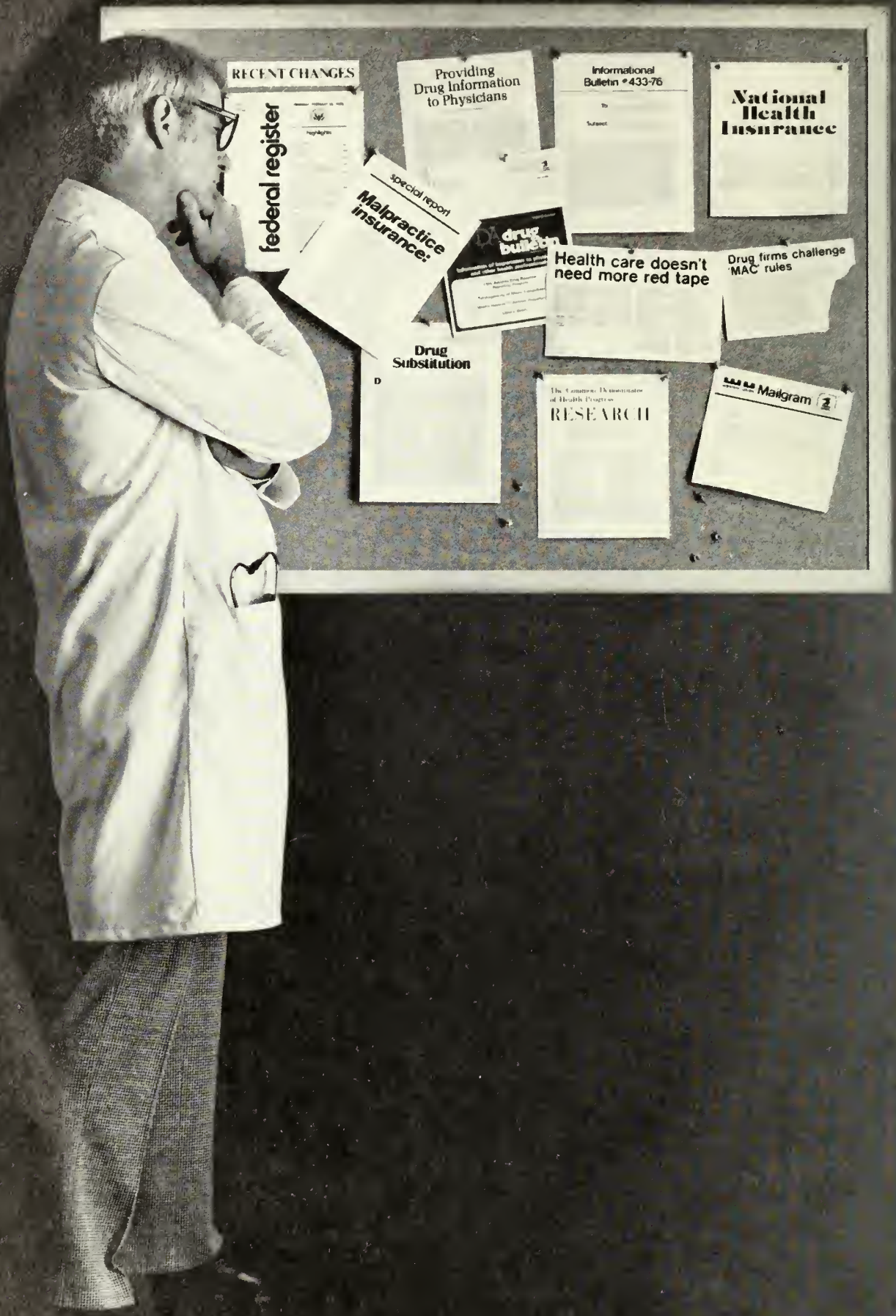
Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005

However you define in acute cystitis achieved an

*In a new study 8 out of 10 patients with acute lower urinary tract infection, primarily cystitis, achieved sterile urine. All infections were nonobstructed. Susceptible organisms included *E. coli, Klebsiella-Aerobacter, Proteus mirabilis* and *Proteus vulgaris.*

No. of patients	Sterile urine	Clear culture <1000 organisms/ ml urine	Clear culture <10,000 organisms/ ml urine
406	81% (330)	83% (339)	88% (357)

Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey

clear culture

Gantanol® B.I.D.
(sulfamethoxazole)

81% to 88% cure rate*

Gantanol® B.I.D.
sulfamethoxazole/Roche

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

Basic therapy with convenience and economy in acute nonobstructed cystitis†

†due to susceptible organisms

ROCHE

Please see following page for summary of product information.

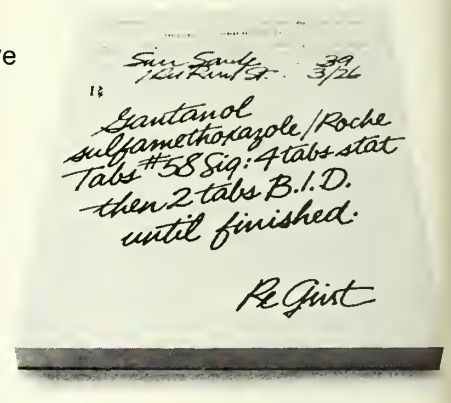
Gantanol® B.I.D.

sulfamethoxazole/Roche

Basic therapy with convenience and economy in acute nonobstructed cystitis*

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

- Effective in nonobstructed cystitis.
- Active against susceptible strains of gram-negative and gram-positive organisms: *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*
- Rapid antibacterial blood and urine levels—in from 2 to 3 hours.
- Convenient, economical B.I.D. dosage.
- Contraindicated during pregnancy and the nursing period and in infants under 2 months of age.
- As with all sulfonamides, adequate fluid intake should be maintained during therapy; perform frequent CBC's and urinalyses with careful microscopic examination.



*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily nonobstructed pyelonephritis, pyelitis and cystitis) due to susceptible organisms, usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.* **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, apla tic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergi reactions* (erythema multiforme, skin eruptions, epidermal necrol sis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scle injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepa titis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactior* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneo reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides ha caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-te administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimeth amine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of bod weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

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Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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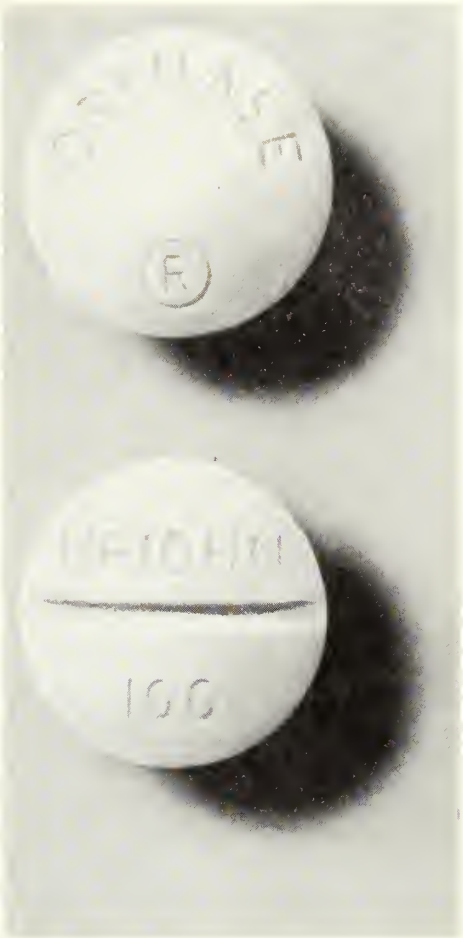

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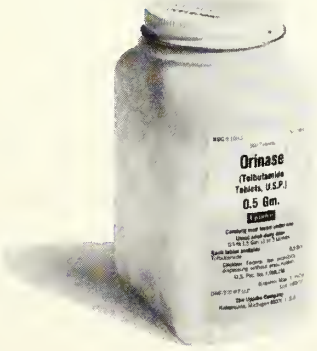
tolbutamide, Upjohn

0.5 Gm tablets



This new design will help pharmacists, physicians, nurses, and patients identify Orinase by name and manufacturer. The number on the tablet is for identification and is not related to tablet strength.

You may wish to advise your patients that this change is taking place.

J-5255-6

The Upjohn Company, Kalamazoo, Michigan 49001 **Upjohn**

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DYAZIDE®

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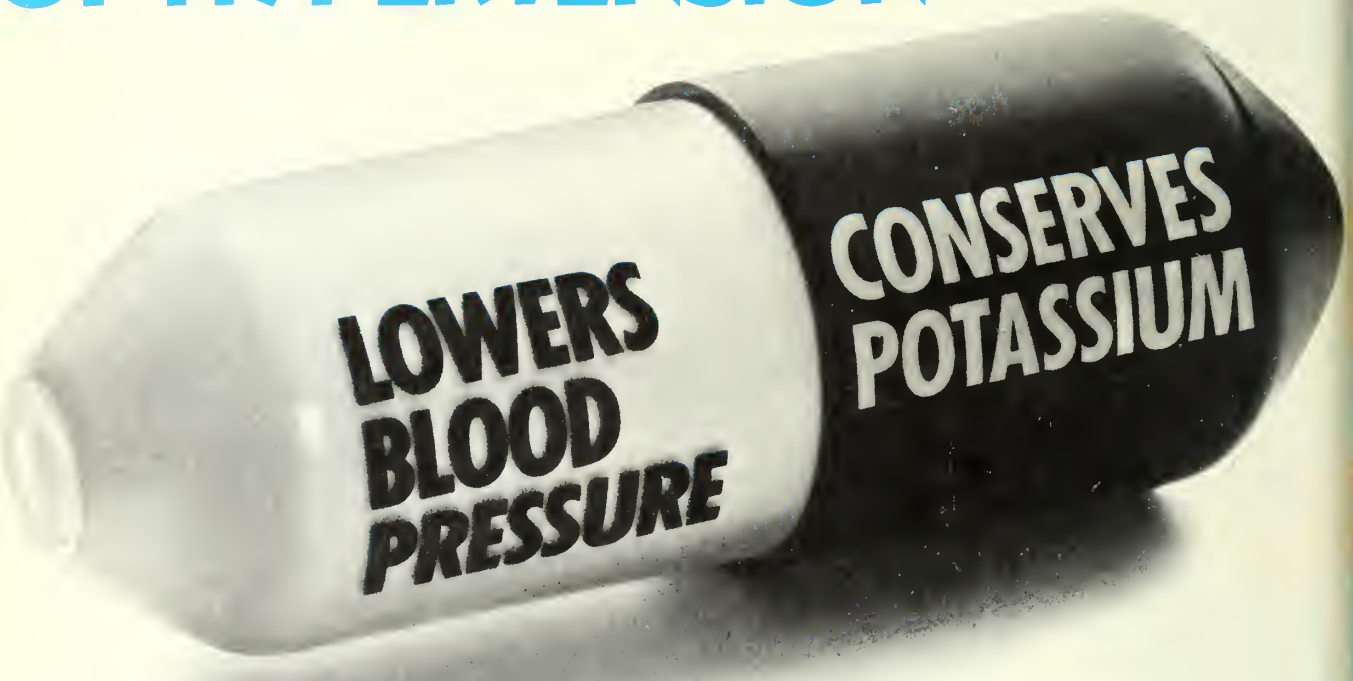
Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

MAKES SENSE FOR LONG-TERM CONTROL OF HYPERTENSION*



Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F CO., Carolina, P.R. 00630
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TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

How many of your patients know what calcium is?

But they do know what milk is.

These dairy foods have several nutrients in common. The principal one is bone-building calcium, which also helps control muscle action and aids in clotting of the blood. Because they all contain calcium, protein and riboflavin, these foods are considered a part of the Milk Group in the U.S. Department of Agriculture's Four Food Groups system.

Some physicians counsel patients in terms of nutrients. Which is easier for them to understand—foods or nutrients?

For attractive, color copies of the Four Food Groups guide for your patients, write: Dairy Council of California, Box 28F, Sacramento, CA 95825.

Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

VISUAL FOCUS ON ACUTE GOUTY ARTHRITIS

Foot of patient with acute gouty arthritis as seen by conventional x-ray.

Scintiphotogram of same foot reflects inflammatory process.

The scintiphotograph on the right shows increased uptake of radiotechnetium polyphosphate in the metatarsophalangeal joint and the proximal interphalangeal joint of the great toe of a patient with acute gouty arthritis. This increased uptake probably results from increased vascularity in the affected areas.

For a more detailed description of scintiphotography, see "addendum" at right.

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CAPSULES, 25 mg and 50 mg

INDOCIN®

(INDOMETHACIN | MSD)

helps relieve pain and other symptoms of inflammation in acute gouty arthritis in selected patients

INDOCIN is a potent drug with anti-inflammatory, antipyretic, and analgesic properties. It should not be used in conditions other than those recommended. Although INDOCIN does not alter the progressive course of the underlying disease, in selected patients with acute gouty arthritis it has been found highly effective in relieving pain and in reducing fever, swelling, and tenderness.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

addendum

MSD
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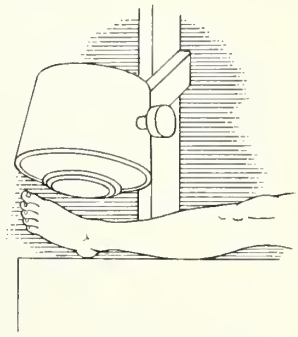

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THE WESTERN
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Polyps and Cancer of the Large Bowel

BASIL MORSON, MD, *London*

MORTALITY STATISTICS tell us that cancer of the colon and rectum is second only to lung cancer as a cause of death in the general population of England and Wales[1] but when its relatively much higher cure rate is taken into consideration then the incidence rates of lung and bowel cancer may be very similar. Statistics from the United States have shown that large bowel cancer is becoming commoner and now has a higher incidence in the total population than any other type of cancer except cancer of the skin.[2] Cancer of the colon and rectum is therefore an important public health problem.

It is well recognized that the identification of precancerous conditions is the basis of cancer prevention. At the present time isolated adenomas, familial polyposis and ulcerative colitis are the conditions that are known to predispose to cancer of the large bowel. The concept that most cancers of the colon and rectum evolve from isolated adenomatous polyps and villous adenomas is sometimes known as the polyp-cancer or adenoma-carcinoma sequence.

Granted that a substantial body of evidence in support of the polyp-cancer sequence is already available[3,4] the following questions require to be answered in detail:

(1) Do all adenomatous polyps and villous adenomas inevitably become cancerous? (2) Does all cancer of the colon or rectum evolve from preexisting adenomatous polyps and villous adenomas? (3) How long does it take for the adenoma-carcinoma sequence to evolve? (4) If some cancer does not arise from preexisting adenomas, what is the alternative mechanism of histogenesis?

Aspects of the morphology of the adenoma-carcinoma sequence will be described here, together with some statistics from St. Mark's Hospital, London, about the malignant potential of isolated adenomatous polyps and villous adenomas. Other evidence will also be presented which gives some idea of the life history of the adenoma-carcinoma sequence.

Morphology of the Adenoma-Carcinoma Sequence

It is common to see neoplastic tumors in the colon and rectum that are partly benign and partly malignant. This can be obvious on gross examination. Sometimes, however, the benign or malignant component may only be apparent as a result of microscopic studies. A macroscopically benign adenomatous polyp or villous adenoma should always be carefully examined for evidence of invasive cancer because the latter may be limited to small microscopic foci. Occasionally, what appears to be a benign adenomatous polyp is found to be entirely composed of cancer on microscopic examination (so-called polypoid carcinoma). Whatever their relative proportions the presence of contiguous benign and malignant tissue is some evidence that the carcinoma arose from a previously benign adenoma.

In a series of 1,961 malignant tumors in patients seen at St. Mark's Hospital from 1957 to 1968, there were 278 (14.2 percent) in which there was evidence of contiguous benign tumor, either adenomatous polyp or villous adenoma. The frequency with which benign adenoma is found in continuity with cancer varies with the extent of spread of the malignant component. If the latter shows spread into the extramural tissues of the wall of the colon or rectum the frequency with which benign tumor is found is only 7 percent. With spread in continuity limited to the wall

From the Department of Pathology, St. Mark's Hospital, London.

Presented as the Centennial Lecture in Pathology at Children's Hospital and Adult Medical Center, San Francisco, July 29, 1975.

Some of this work was carried out by Dr. T. Muto during his appointment as a World Health Organization Research Fellow in the Department of Pathology at St. Mark's Hospital.

Submitted January 26, 1976.

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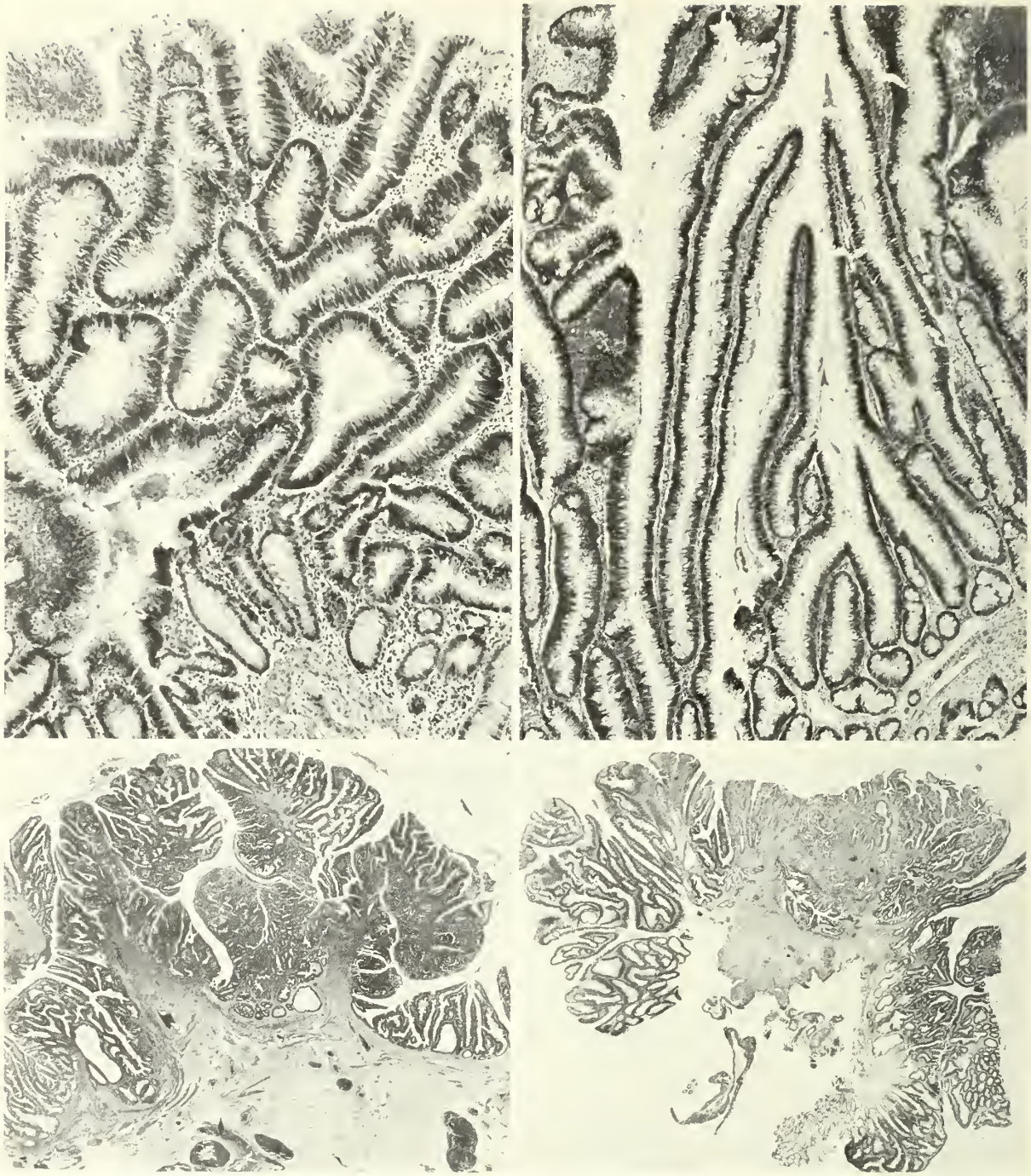

Figure 1.—Upper Left, detail of benign adenomatous polyp showing mild epithelial atypia (reduced from H & E× 126); **Upper Right,** detail of benign villous adenoma showing mild epithelial atypia (reduced from H & E×50); **Lower Left,** tubulovillous (villoglandular) adenoma. In the central part of the photograph there is severe epithelial atypia but the neoplastic glands have not actually crossed the line of the muscularis mucosae (reduced from H & E×15); **Lower Right,** tubulovillous adenoma. In the central part of the specimen there is severe epithelial atypia with invasion by adenocarcinoma across the line of the muscularis mucosae into the submucosal tissues. The adenoma is in continuity with the adenocarcinoma (polyp-cancer sequence) (reduced from H & E ×15).

of the bowel it rises to nearly 20 percent, but if there is invasion of the submucosal tissues only it is nearly 60 percent. This approach to the study of the adenoma-carcinoma sequence suggests that certainly about half and probably nearer two thirds of all cancer of the colon and rectum arises from previously benign adenomatous polyps or villous adenomas. It is probable that as cancer spreads through the bowel wall so it expands on the mucosal surface and tends to destroy surviving benign tumor.

Malignant Potential of Adenomatous Polyps and Villous Adenomas

Adenomatous polyps, villous adenomas and their synonyms are names given to describe different histological types of benign neoplastic polyp (see Figure 1). There is a histological spectrum with the typical adenomatous polyp (tubular adenoma) at one end and the typical villous adenoma (villous papilloma) at the other. The intermediate histological type has been called "papillary" adenoma, "villoglandular" or "tubulovillous" adenoma. Whatever the name used, the histological structure is intermediate between adenomatous polyp and villous adenoma and will be described as such here.

The adenomatous polyp (75 percent) is far more common than the typical villous adenoma (10 percent) and about 15 percent of tumors have an intermediate structure. The malignancy rate for the different histological types of polyp can be assessed by an analysis of the frequency with which cancer is found in a series of tumors that are either wholly or partly benign. *In this context "cancer" is defined as invasion across the line of the muscularis mucosae.* The general malignancy rate for the common adenomatous polyp is only 5 percent compared with 40 percent for villous adenomas. The intermediate type of polyp (usually called villoglandular adenoma in the United States) at 22 percent seems to behave more like the villous growth pattern than the adenomatous polyp. These figures emphasize that villous adenomas have much the greatest malignant potential. How can this be explained?

It has been clear for many years that there is a close relationship between the size of adenomas and their malignant potential. The St. Mark's experience shows that the malignant potential of adenomatous polyps and villous adenomas (including the intermediate type) is very low indeed for tumors under 1 cm in diameter; between 1 and 2 cm in diameter the malignancy rate increases to one in ten, but nearly half of all polyps over 2 cm in diameter contain evidence of invasive cancer. These figures obviously have great practical importance for radiologists, surgeons and pathologists.

The common adenomatous polyp is usually small and very rarely contains invasive cancer.[5] As they grow, however, so the malignant potential increases and about a third of them over 2 cm in size are malignant. But, even small villous adenomas have a malignancy rate of about 10 percent and cancer is found in about 50 percent of those over 2 cm in diameter. The malignancy rate for the intermediate histological type approaches much closer to that for villous adenomas than for adenomatous polyps. Mostly, the villous type of growth pattern presents as a larger tumor than the ordinary adenomatous polyp.

Although there are important differences in the frequency and behavior of adenomatous polyps, villous adenomas and the intermediate histological type, it must be emphasized that the cytological characteristics in all three varieties are the same. It is essential to distinguish between the histology or tissue architecture of these tumors and their cellular features. It is customary to regard the latter as an epithelial atypia or dysplasia which can be graded as mild, moderate or severe. Many histopathologists would regard severe dysplasia as synonymous with carcinoma *in situ*. However, this is an expression best avoided in the diagnostic practice of tumors of the colon and rectum because of its controversial meaning.

The grade of atypia in polyps is not always uniform and foci of severe dysplasia may be seen in a tumor which otherwise has mild or moderate dysplastic changes. The criteria for judging the degree of epithelial atypia include nuclear changes such as enlargement and pleomorphism, loss of polarity, stratification and an increase in the number of mitotic figures, some of which may be abnormal forms. With increasing severity of dysplasia there is loss of differentiation and usually, but not invariably, a decreasing amount of mucin secretion. The diagnosis of malignancy is made only by observing invasion across the line of the muscularis mucosae. Once this barrier has been breached there is potential for metastasis, although a distinction must be made between true cancer and pseudocarcinomatous invasion.[4]

The grade of epithelial atypia is valuable in the study of the malignant potential of adenomatous

polyps and villous adenomas. Mild atypia is associated with a low malignant potential, but a third of all polyps with severe atypia contain invasive cancer. In other words, there is a clear correlation of increasing epithelial atypia with increasing malignant potential. The St. Mark's figures[5] also show that small polyps very rarely show severe atypia but when they do there is a high malignant potential. But as polyps get larger the influence of the degree of atypia on malignant potential is diminished. Size seems to have paramount importance in judging the risk of cancer.

The relationship of grade of atypia to histological type of polyp is also interesting.[5] The malignancy rate for all adenomatous polyps with mild or moderate atypia, which are the great majority, is low. Severe atypia in adenomatous polyps is uncommon but is associated with a relatively high malignant potential (about 25 percent). Villous adenomas, on the other hand, often show severe atypia and this may be one important explanation for their high malignant potential compared with that of adenomatous polyps.

Multiple Benign and Malignant Tumors

There is abundant evidence that most cancers of the colon and rectum arise from previously benign adenomatous polyps and villous adenomas.[3,6-8] Granted the importance of this relationship, a study of multiple benign and malignant tumors gives useful information about groups of patients who are at increased risk from neoplastic disease of the large bowel. Of a total of 3,002 patients at St. Mark's there were 2,412 who had one tumor only and 590 (19.7 percent) who had multiple synchronous tumors, either benign or malignant. This means that one in five of all patients with neoplastic disease of the large bowel have more than one benign or malignant tumor somewhere in the colon or rectum. This fact has important clinical implications. It means that meticulous examination of the whole large intestine is essential for patients who have presented with a tumor in one part of it.

In the same series of 3,002 patients there were 210 (7 percent) in whom a second or metachronous benign or malignant tumor was found to have developed when subsequent follow-up examinations were made. It is probable that this figure is an underestimate because this study covers a period of time before the introduction of colonoscopy. Moreover, in not all the patients were sufficiently meticulous follow-up examinations by air contrast barium enema carried out—which is essential for proper investigation of the whole colon. It is likely that the risk of a second tumor developing is at least one in ten and probably greater. This also illustrates the importance of follow-up of all patients who have had an adenomatous polyp, a villous adenoma or a cancer removed from any part of the large intestine. Studies at St. Mark's have also shown that the risk of developing cancer increases with the number of benign adenomatous polyps or villous adenomas. At this point, the important distinction between polyps that are genuine adenomas and those that a histopathologist can recognize as hyperplastic or metaplastic polyps must be emphasized. The latter have no relationship to cancer.

Metachronous Cancer of the Colon and Rectum

Patients in whom a malignant tumor has been removed from one part of the large bowel are at risk for a further malignant tumor developing in any remaining large intestine.[9,10] The interval between the first and second malignant tumor varies from 2 to 31 years in the St. Mark's series, with an average of 13.5 years. The cumulative risk of developing a second malignant tumor increases with the length of follow-up, reaching about 5 percent after 25 years, but the risk varies according to whether or not adenomatous polyps or villous adenomas were present in the first operation specimen. If they were present then the risk of a second malignant tumor rises steeply with time to reach 10 percent at about 25 years. In the absence of such polyps in the first specimen the curve flattens off to a metachronous cancer rate at 25 years of only about 4 percent. This is evidence, first, that there is an important relationship between adenomas and cancer, but, second, it suggests that the adenoma-carcinoma sequence is probably a process that evolves for many years.

Life History of the Adenoma-Carcinoma Cancer Sequence

The actual time it takes for the adenoma-carcinoma sequence to evolve can be measured by a study of the age distribution curves of patients with adenomas and cancer. These show that adenomas appear on the average about four years before cancers. This figure must be a considerable

underestimate because whereas the age at diagnosis of cancer may be fairly accurate, the age at diagnosis of a polyp is likely to be very approximate because usually there are no symptoms. Further comment about the value of age distribution curves as applied to the adenoma-carcinoma sequence is given below under the heading of Familial Polyposis.

It is rarely possible to make direct observations on the adenoma-carcinoma sequence because polyps are usually removed by local excision. The fate of four patients with adenomatous polyps in the rectum who refused treatment has been studied. In the first two cases the diagnosis of cancer was made about five years later. In the third case the polyp-cancer sequence took longer than 12 years to evolve. The case of the fourth patient illustrates the observation that a histologically proven adenomatous polyp may remain benign for at least 10 years without becoming malignant. It has already been shown that the malignancy rate for all adenomatous polyps is only about 5 percent, which of course suggests that many, and probably most, adenomatous polyps never evolve into cancer.

It is easier to make direct observations over a long period of time on villous adenomas because these are usually large tumors that are prone to recurrence after local excision. Our studies have found that villous tumor, proven histologically, will remain benign for up to 20 years without becoming malignant. In one patient benign tumor only was observed for nearly 30 years before malignant change was detected. In another patient the evolution of the polyp-cancer sequence took at least ten years. In all these patients repeated local excisions for benign tumor had been done at the same site in the rectum and it is, of course, possible that this delayed the onset of malignancy. Although it has already been shown that villous adenomas have a high malignant potential it is likely that the adenoma-carcinoma sequence, as judged by this evidence, evolves over many years and as with adenomatous polyps, it is likely that some villous adenomas may never become cancerous.

The life history of the adenoma-carcinoma sequence is probably very variable. The study of metachronous cancer rates, age distribution curves and these direct, if selected, observations suggests that it is never less than 5 years and is, on the average, about 10 to 15 years, but may even cover a normal adult life span. Further support for this opinion is obtained from a study of the adenoma-carcinoma sequence in Familial Polyposis.

The Adenoma-Carcinoma Sequence in Familial Polyposis

In this genetically predetermined condition the mucous membrane of the large intestine is covered by hundreds or thousands of adenomas. Mostly these have the structure of tubular adenomas (adenomatous polyps) but it is not sufficiently well recognized that a minority are villous and others have an intermediate histological structure. In patients with familial polyposis, cancer will almost inevitably develop if left untreated and all the evidence suggests that the cancer arises from the adenomas.[11]

A study of the life history of the adenoma-carcinoma sequence in familial polyposis gives very useful information which is relevant to our ideas about the time it takes for cancer to evolve from isolated adenomatous polyps or villous adenomas. For example, the age distribution curves for polyposis and cancer show that the average age at diagnosis of polyposis without cancer is about 27 years and polyposis with cancer about 39 years. This gives a time interval of about 12 years between the diagnosis of polyposis and the later development of cancer. As with the age distribution curves for isolated adenomas and cancer, measurement of the age at onset of polyposis is inaccurate but probably much less so than for isolated lesions. In any case the figure of 12 years is likely to be an underestimate of the length of the adenoma-carcinoma sequence in these circumstances.

More information about the time it takes for cancer to develop in patients with polyposis comes from analysis of the age at onset of polyposis and cancer in 59 patients who, for one reason or another, did not have any treatment for their disease. Mostly these patients were under care at St. Mark's Hospital before the operation of total colectomy and ileorectal anastomosis was established about 25 years ago. Findings in this study have shown that out of 59 patients with polyposis observed during five years, in only seven (12 percent) did cancer develop. There were, then, 52 patients who harbored adenomas for five years without malignant change. The cancer rate between five and ten years increased to 25 percent, but there were still 29 patients who had had adenomas for ten years that remained

benign. At 10 to 15 years the cancer rate increased to just over 30 percent and there were still 13 patients who had had adenomas for 15 years without any malignant change. The cancer rate at 15 to 20 years was over 50 percent but four patients had polyposis for 20 years that remained benign. Lastly, there were three patients in whom the adenoma-carcinoma sequence took over 20 years. These figures lend support to the concept that the evolution of cancer of the colon and rectum from adenomatous polyps and villous adenomas takes at least 5 years and maybe more than 20 years, but on the average lies between 10 and 15 years. It must also be remembered that only one or a few malignant tumors develop in polyposis and that most of the adenomas in this condition do not become malignant during a normal life span. It has already been shown that the malignancy rate for adenomatous polyps is only about 5 percent, and for villous adenomas about 40 percent. This must mean that many adenomatous polyps and villous adenomas never become malignant.

For many years it has been customary at St. Mark's to treat patients with familial polyposis by total colectomy and ileorectal anastomosis. The adenomas in the rectum are removed by fulguration and recurrences of benign tumor at subsequent follow-up examinations are also treated by this method. The risk of cancer in the rectal stump after colectomy and ileorectal anastomosis has been analyzed for 86 patients followed for up to 25 years.

So far only in two patients has cancer of the rectum developed at two and seven years after colectomy. The longest follow-up is for 11 patients who have remained free of cancer for between 20 and 25 years. This low incidence of cancer of the rectum after colectomy and ileorectal anastomosis at St. Mark's is in great contrast to that reported from the Mayo Clinic[12] and requires some explanation. It may be significant that the rectal stump was kept free of adenomas by fulguration in all the St. Mark's patients. In other words, removal of adenomas means prevention of cancer. It is also possible that the operation of total colectomy and ileorectal anastomosis so changes the environment of the rectal mucosa that neoplastic activity is inhibited. Hence, perhaps, the observation of regression of adenomas in the rectum after this operation. The high cancer rate in the rectum in the Mayo Clinic series may, however, be explained by different methods of selection and management of patients with polyposis.

Conclusions

At the beginning of this discussion four questions were asked for which answers can now be attempted.

First, do all adenomatous polyps and villous adenomas inevitably become cancerous? The answer must be no, if only because the prevalence of these tumors is so much greater than the prevalence of cancer. Evidence has been presented that shows that the risk of cancer varies with the size of the adenoma, with its histological type and the degree of epithelial atypia. Generally speaking, the risk of cancer is very low indeed for tumors under 1 cm in diameter but increases to 50 percent when the adenoma is over 2 cm in diameter. Villous adenomas are usually larger than adenomatous polyps.

Villous adenomas have considerably greater malignant potential than adenomatous polyps. Apart from the important issue of size, it has been shown that the cancer rate increases with the degree of epithelial atypia and severe atypia is more common in villous adenomas than in adenomatous polyps. However, the evidence also suggests that many adenomatous polyps and villous adenomas never become malignant.

Second, does all cancer of the colon and rectum evolve from preexisting adenomatous polyps and villous adenomas? The evidence suggests that most cancer of the colon and rectum has evolved through the adenoma-carcinoma sequence. The answer to the fourth question posed at the start can be conveniently answered now. If some cancer does not arise from adenomatous polyps and villous adenomas what is the alternative mechanism of histogenesis?

The concept of cancer "de novo" is difficult to appreciate because it has never been defined in morphological terms. It must be understood that adenomas can be very flat, although clearly circumscribed lesions which are only very slightly raised up above surrounding normal mucous membrane. However, it is rare for them to adopt this form in the colon and rectum. More often they are obviously elevated to form a "polyp," sessile or pedunculated. Whatever its gross appearance adenoma is the only known precursor of cancer of the large bowel other than the more diffuse and extensive epithelial changes seen in long-standing ulcerative colitis. For pathologists,

of course, familial polyposis should be more accurately called "adenomatosis."

How long does it take for the adenoma-carcinoma sequence to evolve? It is not possible to give an accurate answer, but the study of the behavior of patients with isolated adenomas and familial polyposis suggests that the polyp-cancer sequence evolves slowly. On the average it takes 10 to 15 years; it may take as little as 5 years or as long as 25 years.

Because adenomatous polyps and villous adenomas have significant potential for malignant change every opportunity should be taken to discover and remove them. At a time when the surgical cure rate for cancer of the colon and rectum shows no sign of improvement prevention becomes an issue of great clinical importance. The introduction of the double contrast barium enema and the colonoscope means that we can now accurately examine the entire large bowel.

Patients who have had adenomas or cancers removed have a significantly increased risk of further adenomas or cancer developing in any remaining large intestine and should therefore have regular follow-up examinations by air contrast barium enema or colonoscopy, whichever is clinically appropriate. Study of the life history of the adenoma-carcinoma sequence suggests that these follow-up examinations can be done at three yearly intervals provided the patient's large bowel was tumor-free at the last examination. It is only by persistent follow-up and meticulous examination of the whole large bowel that a significant measure of cancer prevention will be achieved.

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Diagnosis and Treatment of Amanita Phalloides-Type Mushroom Poisoning

Use of Thioctic Acid

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The number of cases of mushroom poisoning is increasing as a result of the increasing popularity of "wild" mushroom consumption. Amanitin and phalloidin cytotoxins found in some Amanita and Galerina species produce the most severe and frequent life-threatening symptoms of Amanita phalloides-type poisoning. Delay in onset of symptoms, individual susceptibility variation and lack of rapid and reliable identification have contributed to the significant morbidity and mortality of this type of poisoning.

A rapid chromatographic assay for identifying the potent cytotoxins and apparently successful management using thioctic acid of two cases of A. phalloides-type mushroom poisoning are reported. All known cases of A. phalloides-type mushroom poisoning treated with thioctic acid in the United States are summarized.

THE GATHERING AND EATING of wild mushrooms is a popular pastime in the United States, partly owing to increased interest in "organic" foods and in the hallucinogenic substances found in certain species. Severe and life-threatening poisonings from the ingestion of wild mushrooms have increased in frequency. Of the 2,000 or so species of mushrooms known to exist, fewer than 50 are poisonous to man.[1] Many mushroom hunters believe that poisonous varieties can be identified easily[2,3] and many have the erroneous notion that some toxic species can be rendered harmless by cooking in a particular manner. As a result, even experienced mushroom seekers have been stricken when they harvested and ate poisonous varieties.

From 1957 to 1964, 30 deaths from ingestion of wild mushrooms were reported in the United States; 11 of these occurred in California.[2] From 1964 to 1974, 57 cases of mushroom poisoning, including eight deaths, occurred in California alone (Table 1); 18 of the poisonings and four of the deaths occurred in 1972.

The principal toxins of the most poisonous mushrooms are complex proteins containing

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TABLE 1.—*Summary of Known Cases of Mushroom Poisoning in California from 1964 to 1974 (57 Cases)*

No. of Cases	*Age(s) Sex(es)*	*California County Where Mushrooms Were Picked*	*Genus and Species of Mushroom*	*Date Ingested*	*Onset of Symptoms After Ingestion (hr)*	*Initial Symptoms**	*Treatment*	*Outcome*
17	10-60 ♂&♀	Los Angeles	Chloraphyllum molybdites	9-13-64	1½-2	GI, fever, headache, diaphoretic	Supportive care	Recovered
1	46♂	Marin	Amanita phalloides	11-?-68	Several	GI, shock	?	Died
2	50♂, 15-18♂	Sierra	?	6-?-68	?	GI, prostration	Atropine, supportive care	Recovered
2	78♂, 80♀	San Joaquin	?	9-?-68	1½-2	GI	Atropine, supportive care	Recovered
2	50♂, 80♀	San Joaquin	Boletus eastwoodii	3-?-69	1½-2	GI	Atropine, supportive care	Recovered
1	72♂	Marin	A. phalloides	12-?-70	Several	GI, shock	?	Died
1	59♀	Marin	A. phalloides	1-1-72	6-8	GI	?	Died
2	45♂, 44♀	San Francisco	?	5-9-72	?	?	?	Recovered
7	20-29 ♂&♀	Nevada	B. eastwoodii	1-22-72	1½	GI, prostration, cramps, bradycardia	Atropine, supportive care	Recovered
1	41♂	Santa Cruz	A. phalloides	11-5-72	12-24	GI, abdominal pain, shock	?	Died
4	14♂, 52♀†	Santa Cruz	A. phalloides	11-5-72	6-12	GI, abdominal pain, shock	Supportive care, thioctic acid	2 recovered, 2 died‡
1	31♀	San Mateo	A. phalloides	11-12-72	12	GI, abdominal pain	?	Recovered
2	74♂, 74♀	Sacramento	A. phalloides	11-12-72	14	GI, abdominal pain, prostration	?	Recovered
1	63♂	Sonoma	A. phalloides	12-30-72	13	GI, abdominal pain, prostration, dehydration	?	Recovered
1	30♂	Fresno	A. phalloides	3-21-73	Several	GI, weakness	Supportive care	Recovered
1	32♂§	Fresno	A. phalloides	3-2-73	12	GI, weakness, fever?	Thioctic acid, supportive care	Recovered
2	20♂, 30♂	Santa Cruz	A. phalloides	10-30-73	10-15	GI, shock, jaundice seizure	?	1 died, 1 recovered
2	20♀, 30♂	San Joaquin	A. phalloides	5-27-74	Several	GI, cramps	Supportive care	Recovered
1	21 mo.♂	San Joaquin	A. phalloides	5-27-74	Several	GI, cramps	Supportive care	Died
3	40♂, 18♀, 39♀	Orange	Chloraphyllum molybdites	8-22-74	½-3	GI, cramps, weakness, abdominal cramps and pain	?	Recovered
1	23♂¶	Sonoma	C. molybdites	9-?-74	2	GI (no diarrhea)	Supportive care, thioctic acid	Recovered
1	33♂**	Marin	A. phalloides	11-?-74	Several	GI	Thioctic acid, supportive care	Recovered
1	87♂††	Santa Clara	A. phalloides	12-16-74	22	GI, cramps	Thioctic acid, supportive care	Recovered

*GI = nausea, vomiting and diarrhea.
†One is Case No. 11 in Table 3.
‡Death in one who received thioctic acid.
§Case No. 1 in Table 3.
¶Case No. 4 in Table 3.
**Case No. 3 in Table 3.
††Case No. 2 in Table 3.

TABLE 2.—*Diagnosis of Mushroom Poisoning*

Cause	*Toxic Constituents*[1,10]	*Genus and Species*	*Comments*
Cellular Toxins	Amanitins Phalloidins	Amanita (Sp. phalloides, verna, virosa)	Found mostly in wooded areas, frequently during late summer and fall seasons. No obnoxious taste or smell. Gastrointestinal symptoms occur 6 to 24 hours after ingestion. A transient period of improvement is followed by metabolic disturbances and renal and hepatic impairment. Most fatalities occur within several days. As little as one third of a single cap can be fatal in a child. Mortality is 40 to 90 percent. These species of Amanita account for nearly 90 percent of all cases of severe mushroom poisoning.
	Amanitins	Galerina (Sp. autumnalis, marginata, venenata)	These species are found in the western and midwestern United States on lawns, meadows, and decaying wood. Symptoms are similar to those of A. phalloides-type poisoning. Despite absence of the phalloidin toxin, the mortality risk from ingestion of these species should be considered as significant as for A. phalloides due to presence of amanitin.
Enzyme Toxins	Monomethyl-hydrazine (Gyromitrin)	Gyromita (Sp. esculenta) Helvella (Sp. esculenta, underwoodii)	These species (except underwoodii) are not confined to any particular habitat or geographic region. These mushrooms produce symptoms similar to intoxication by amanitin but less severe, appearing 6 to 12 hours or more after ingestion. Symptoms are primarily gastrointestinal. Hemolysis and central nervous system effects are associated with these mushrooms. Certain people are resistant to their effects. Cooking may attenuate toxicity. Estimated mortality is 2 to 4 percent.
Neurologic Toxins	Muscarine	Inocybe (Sp. napipes) Clitocybe (Sp. rivulosa, trunicola, cerussata, olearia, dealbata)	Toxins produce "muscarinic" effects, e.g. salivation, lacrimation, nausea, bronchospasm, abdominal pain, vomiting, diarrhea, headache and miosis within 15 to 30 minutes after ingestion. Bradycardia, hypotension and shock may also occur. Death is infrequent. Treatment is primarily supportive and symptomatic. Atropine is a specific antidote for muscarine intoxication. There appear to be species differences because only some have caused death.
	Isoxazole Derivatives: Muscimol Muscazone Ibotenic Acid Pantherin Tricholomic Acid	Amanita (Sp. muscaria, pantherina, cokeri, crenulata, solitaria)	Commonly found in wooded areas, especially conifer forests of western United States in spring and fall. These mushrooms are also known as "fly mushroom" or "fly agaric." These species have been associated with the toxin muscarine, but in fact contain toxicologically insignificant quantities of it. They produce symptoms resembling the central nervous system effects of excessive atropine and display anticholinergic and mild hallucinogenic properties. Symptoms occur within ¼-2 hours after ingestion and frequently resemble alcohol intoxication. Severity and duration of symptoms vary with individual. Muscle spasms can occur after ingestion of large quantities. Prognosis for recovery is good. Avoid use of sedatives; atropine is contraindicated in treatment. Death is rare.
	Psilocybin Psilocin	Psilocybe (Sp. cubensis, caerulescens, silvatica) Panaeolus (Sp. foenisecii	Psychotropic "LSD-like" manifestations begin about 30 to 60 minutes after ingestion and may continue for several hours. Recovery is spontaneous and usually within a day. Treatment is symptomatic.

TABLE 2.—*Diagnosis of Mushroom Poisoning (Continued)*

Cause	*Toxic Constituents*[1,10]	*Genus and Species*	*Comments*
Gastrointestinal Irritants	Not Yet Identified	*Boletus (Sp. satanas, eastwoodii) Clitocybe (Sp. nuda, illudens) Chlorophyllum (Sp. molybdites) Russula (Sp. emetica) Tricholoma (Sp. venenatum, pardinum) Catharellus (Sp. floccosus) Hebeloma (Sp. crystuliniforme) Lactarius (Sp. torminosus, glaucescens) Naematoloma (Sp. fasciculare) Rhodophyllus (Sp. sinuatus)	Irritating constituents have not been identified. Probably many toxins are involved. Mild to severe nausea, vomiting, diarrhea, abdominal cramps, and other gastrointestinal symptoms occur ½ to 2 hours after ingestion and may persist for several hours. The incidence and severity of gastrointestinal symptoms are greater with raw mushrooms. Treatment is supportive, and symptoms usually terminate spontaneously within a short time. Rare fatalities have been reported.
Disulfiram-like Constituents	Monomethyl-hydrazine	Coprinus (Sp. atramentarius)	Disulfiram reaction-like symptoms of flushing, palpitation, hyperventilation and tachycardia occur only if alcohol is consumed in combination with these mushrooms. These effects may take place up to 48 hours between ingestion of mushroom and alcohol and last for a short time. Gastrointestinal symptoms of nausea, vomiting, and diarrhea have also occurred. The severity of symptoms is greatest after ingestion of raw mushrooms. Treatment is supportive and alcoholic beverages should be avoided.

*These species have been the most frequently associated with gastrointestinal irritants.

cyclic heptapeptides (phalloidins) and cyclic octapeptides (amanitins).[4] Phalloidin appears to disrupt hepatic cell membranes and to change the structure of the hepatic endoplasmic reticulum adversely. The role of phalloidin in the production of symptoms and pathologic changes in the liver of a poisoned patient is unclear because some species now known to contain this cyclopeptide and no amanitin have been consumed without causing the undue effects. The toxicity of amanitin has been compared *in vitro* with that of phalloidin and found to be 10 to 20 times greater. The amanitin is believed to be the major toxin responsible for the symptoms and pathology following the ingestion of Amanita phalloides-type mushrooms. This is best demonstrated by the toxicity of some species of the Galerina mushrooms that contain only amanitin. It has been shown that amanitin inhibits the enzyme ribonucleic acid polymerase II and interferes with the synthesis of messenger ribonucleic acid.[5,6] Histochemical examination of hepatic cells after exposure to amanitin shows the presence of abnormal concentrations of lipids and carbohydrates in the cell nuclei.[7,8] Amanitin is also a direct-acting nephrotoxin that produces necrosis of the distal and proximal convoluted tubules.[9]

Mushrooms containing phalloidin and amanitin belong to the genera Amanita and Galerina, although not all species of these genera contain these toxins (Table 2). In Europe, A. phalloides is the most frequent cause of mushroom poisoning; nearly 90 percent of all such deaths are attributed to A. phalloides, the "death cap."

In the United States, Amanita verna (the "destroying angel"), Amanita virosa and A. phalloides are the common causes of mushroom poisoning and death (90 percent). Recent deaths in California have been attributed to A. phalloides. Cases of severe mushroom poisoning by Galerina marginata, autumnalis and venenata have occurred in this country but are infrequent.[2] Poisoning by the very toxic Amanita and Galerina species will be referred to as A. phalloides-type poisoning in this article.

There appears to be considerable variability in individual susceptibility to the toxins of poisonous mushrooms.[2] For instance, several members of the family of one of our patients (Case 1) ate the meal containing the offending mushrooms, but only one other family member experienced any ill effects. Whether or not there is a quantity-consumed association to development of symptoms is unclear. Severity of symptoms has been thought to depend on the season and the state of maturation of the mushrooms when picked and eaten, the location where they were picked, and the amount ingested.[2] There is no evidence to vali-

date this impression. Approximately 75 percent of the cases in California occurred in the fall, probably coincident to the season when these poisonous mushrooms are most abundant and easily harvested.

During the past three years, we have managed five patients; two are reported here. We consulted in three other cases of severe A. phalloides-type mushroom poisoning. The results of our experience in identifying and treating A. phalloides-type mushroom poisoning are presented.

Diagnosis of Mushroom Poisoning

The time between ingestion and onset of symptoms and the type of systemic involvement (for example, neurologic versus gastrointestinal) can be helpful indexes for characterizing the type of mushroom poisoning. Mushroom poisoning can be divided into cases in which symptoms appear within several minutes to six hours after ingestion and those in which symptoms develop much later (Table 2).

TABLE 3.—*Cases of Mushroom Poisonings Treated with Thioctic Acid (TA) in the United States*

Case No. Age (year) Sex	*Year*	*State*	*Dose of TA and Duration of Treatment*	*Mushroom*	*Method of Identification* (Result)*	*Hospital Course†*
1 . . 32 ♂	1973	California	300 mg × 6 days	Amanita phalloides	TLC (+) mycologist	Refer to Case No. 1 described in text
2 . . 87 ♂	1974	California	100 mg × 1 day then 300 mg × 6 days	A. phalloides	TLC (+) mycologist	Refer to Case No. 2 described in text
3 . . 33 ♂	1974	California	100 mg × 1 day then 300 mg × 6 days	A. phalloides	TLC (+) mycologist	Admitted 12/30. Nausea, diarrhea, and vomiting beginning 12 to 16 hours after ingestion. Severe dehydration on admission. SGOT 728 and 850 and SGPT 1,018 and 2,320 units per ml. Treated with TA, glucose, and supportive measures. SGOT and SGPT returned to normal levels during treatment. Discharged 1/17.
4 . . 23 ♂	1974	California	100 mg × 1 day then 300 mg × 1 day	Chlorophyllum molybdites	TLC (−) mycologist	Admitted 8/26. Abdominal pain, nausea, diarrhea, vomiting, and fever 2 hours after ingestion. SGOT 25, SGPT 20, LDH 210, CPK 70 units per ml, bilirubin (total) 1.0 mg per 100 ml. Treated with TA, glucose, and supportive measures. Discharged 8/29.
5 . . 40 ♀	1974	New York	100 mg × 1 day then 300 mg × 4 days	Galerina autumnalis	TLC (+) mycologist	Admitted 10/30. Severe nausea, vomiting, diarrhea, and abdominal cramps 10 hours after ingestion. BUN 23, serum creatinine 1.2, bilirubin (total) 2.4 mg per 100 ml, SGOT 100, LDH 224 units per ml, urine glucose +1, acetone +1. Treated with TA, glucose, and supportive measures on day 2 of treatment. Course otherwise uncomplicated. Discharged 11/8.
6 . . 50 ♂	1974	New York	100 mg × 1 day then 300 mg × 2 days	G. autumnalis	TLC (+) mycologist	Admitted 10/30. Nausea, vomiting, diarrhea, and abdominal cramps 12 hours after ingestion. BUN 45, serum creatinine 1.8, bilirubin (total) 1.2 mg per 100 ml, SGOT 33, SGPT 36. Treated with TA, glucose and supportive measures. Course uncomplicated. Discharged 11/4.

TABLE 3.—*Cases of Mushroom Poisonings Treated with Thioctic Acid (TA) in the United States (Continued)*

Case No. Age (year) Sex	*Year*	*State*	*Dose of TA and Duration of Treatment*	*Mushroom*	*Method of Identification* (Result)*	*Hospital Course†*
7 . . 71 ♀	1974	Washington	100 mg × 1 day then 300 mg × 5 days	G. autumnalis	TLC (+) mycologist	Admitted 11/21. Nausea, vomiting, profuse diarrhea, tachycardia, and slight abdominal pain 12 to 16 hours after ingestion. Treated with TA, glucose, and supportive measures. Course uncomplicated and laboratory indexes were within normal limits. Discharged 12/1.
8 . . 58 ♂	1972	Ohio	300 mg × 13 days	Amanita virosa	mycologist	Admitted 10/2. Severe hypotension, vomiting, and diarrhea 6 hours after ingestion. BUN 51, serum creatinine 4.5 mg per 100 ml, SGOT 900, SGPT 1,750, LDH 1,920 units per ml, Hct 58%. Complicated course requiring hemodialysis; biopsy revealed acute tubular necrosis, liver function tests returned to normal values at completion of a 13 day course of TA, glucose, and supportive measures. Maculopapular rash and erythema multiforme of unknown etiology developed at completion of TA treatment. Discharged 10/21.
9 . . 24 ♀	1972	Ohio	300 mg × 5 days	A. virosa	mycologist	Admitted 10/3. Nausea, vomiting, and diarrhea of 1½ day duration beginning about 6 hours after ingestion. Treated with TA, glucose, and supportive measures. Course uncomplicated. Discharged 10/12.
10 14 mo ♂	1972	Ohio	300 mg × 1 day	A. phalloides	mycologist	Admitted 10/3. No symptoms. Hepatic and renal functions normal throughout. Treated with TA, glucose, and supportive measures. Course uneventful. Discharged 10/8.
11 . . 52 ♀	1972	California	300 mg × 1 day	A. phalloides	mycologist	Admitted 11/5. Nausea, vomiting, diarrhea, and abdominal cramps developed 12 hours after ingestion. "Improved" on fourth day but then became progressively disoriented and obtundated. TA begun on day 7 after ingestion at "time of cerebral death." Died on 11/14.
12 . . 35 ♂	1970	Pennsylvania	300 mg × 6 days	A. verna	mycologist	Admitted 11/15. Severe abdominal pain, nausea, vomiting, and diarrhea developed 9 hours after ingestion. Treated for 5 days with glucose and supportive measures. Liver function decreased: SGOT 2,000+ units per ml and bilirubin (total) 7.6 mg per 100 ml. Condition complicated by hepatomegaly, ascites, and intermittent coma. TA started on day 8 after ingestion. Liver function tests returned to normal values by sixth day of TA. Liver biopsy showed necrosis with repair. Discharged 12/2.

*TLC = thin layer chromatography.
†SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; LDH = lactic dehydrogenase; CPK = creatine phosphokinase; BUN = blood urea nitrogen, and Hct = hematocrit.

Most nonlethal poisonous mushrooms produce symptoms soon after ingestion, whereas A. phalloides-type mushrooms produce life-threatening reactions 6 to 24 hours after ingestion. However, since a mixture of wild mushrooms is often ingested, early onset of symptoms does not exclude the possibility of more serious poisoning. Poisoning with immediate onset of symptoms is further distinguishable by the type of symptoms; that is, gastrointestinal disturbance, parasympathetic stimulation and hallucinations. Such poisoning is rarely serious, and recovery usually occurs within 24 hours (Table 2).

Symptoms of the more toxic A. phalloides-type mushrooms characteristically occur in three stages. (1) The first stage occurs abruptly, 6 to 24 hours after ingestion: abdominal pain, nausea, vomiting, diarrhea (occasionally bloody) and hematuria. These are frequently accompanied by fever, tachycardia, hyperglycemia, hypotension, dehydration and electrolyte imbalance. (2) During the next 24 to 48 hours (two to three days after ingestion), there appears to be remission of symptoms in the face of progressive deterioration of hepatic and renal function. (3) During the subsequent 24 to 48 hours (three to four days after ingestion), hepatocellular damage and renal impairment progressively worsen, and jaundice, hypoglycemia, oliguria, delirium and confusion develop. Myocardiopathy and coagulopathy may be present, and convulsions, coma and death may occur. The mortality rate varies from 40 to 90 percent.[1,11] Death from A. phalloides-type poisoning is usually the result of hepatic or renal failure or both.[11-13]

Because of the delayed onset of symptoms in A. phalloides-type poisoning, patients frequently fail to associate their symptoms with the ingestion of wild mushrooms. Therefore, a careful history of the patient's activities before onset of symptoms is imperative. Failure to suspect mushroom poisoning, to identify the more toxic A. phalloides-type mushrooms and to implement early treatment contribute to the high morbidity and mortality associated with the ingestion of A. phalloides-type mushrooms.

Morphologic and Toxicologic Identification of Mushrooms

In a suspected case of mushroom poisoning, identification of the species by morphologic characteristics is a formidable task because the appearance of the mushroom may be distorted by handling and cooking. Attempts to identify them retrospectively by collecting mushrooms from the area where the ingested ones were harvested is unreliable because poisonous species frequently grow in immediate proximity to nontoxic ones. Examination of fungus spores in the gastric contents may also be inconclusive. If poisoning by A. phalloides-type mushrooms is suspected, gastric contents, mushroom samples, and stool specimens, if available, should be assayed to verify the presence of the amanitin and phalloidin toxins.

To confirm the diagnosis of mushroom poisoning, we modified a thin-layer chromatographic assay that can rapidly detect the presence of amanitin and phalloidin. (This assay is done in the Toxicology Laboratory at San Francisco General Hospital.) Vomitus, intestinal aspirate, stool or uneaten specimens are dehydrated in a rotovacuum evaporator. Fat is removed by refluxing with benzene in a Soxhlet apparatus. The defatted material is then extracted with methanol. This extract, containing the toxic cyclopeptides, is taken to dryness *in vacuo* and the residue is dissolved in 2 ml of anhydrous methanol. Aliquots of this extract are then spotted on commercially available 0.25 mm silica G-60 thin-layer chromatography plates.

For comparison, extracts prepared from A. phalloides mushroom and 5, 10 and 20 μl of alpha-amanitin and phalloidin (both as 0.1 percent solutions in methanol) are spotted as comparison standards. The thin-layer chromatographic solvent system consists of a mixture of 100 ml of glycol monobutylether, 85 ml concentrated aqueous ammonia and 0.5 ml transcinnamaldehyde. The average time for the solvent front to ascend 12 cm is approximately three hours. The plate while still moist is sprayed with 0.1 percent fluorescamine in methanol. Fluorescamine reacts with the primary amino group of alpha-amanitin to form derivatives that fluoresce as bluish-white spots under ultraviolet light.

These are compared with the standards. The same chromatogram is then sprayed with 0.5 percent transcinnamaldehyde in methanol. The solvent is allowed to evaporate and the chromatogram is exposed for 15 minutes to hydrogen chloride gas. The amanitin and phalloidin appear as bluish- to purplish-colored spots. The chromatogram should be evaluated immediately because the color of the toxins fades rapidly. The solvent system gives average relative distance (rf) values of 0.35 for alpha-amanitin, 0.31 for beta-

amanitin, 0.50 for gamma-amanitin and 0.25 for phalloidin. Alpha-amanitin and phalloidin when applied as pure substances have a minimum detection limit of 50 μg and 80 to 100 μg respectively.

Treatment

Early Modes

No specific treatment of A. phalloides-type poisoning has been available in the past. The only treatment available has been supportive, including correction of fluid, metabolic and coagulation disturbances. Induction of emesis is not beneficial, unless it is done soon after ingestion, because of the long interval between ingestion and the appearance of symptoms. Cathartics and activated charcoal have been recommended,[14] although there is no proof of their usefulness in the treatment of A. phalloides-type poisoning. If used, they should be administered soon after ingestion. Numerous forms of therapy such as exchange transfusion[13] and administration of large doses of corticosteroids[15] or antiphalloidin antisera[16] have been used, but none has been shown to be more effective than supportive care. Hemodialysis has been used successfully to treat renal failure,[12,16-18] but its effectiveness is not attributed simply to the removal of amanitin and phalloidin. These toxins appear to be poorly dialyzable when studied *in vitro;* hemodialysis would not remove them effectively in the poisoning circumstance.

Studies with dogs given up to 0.044 mg of ^{14}C-methyl alpha-amanitin per kg of body weight by intravenous injection showed that after five hours, the concentration in serum fell below detection limit, which is <0.3 percent of the toxin dose administered. After six hours, 85 percent of the radioactivity associated with the toxin could be accounted for in the urine.[19]

Cytochrome C has protected mice given lethal doses of amanitin from symptoms of poisoning.[20] Penicillin, phenylbutazone, chloramphenicol and sulfamethoxazole administered to animals poisoned with amanitin resulted in improved survival rates.[21] It has been suggested that these compounds displace amanitin from plasma albumin binding sites, thus enhancing renal excretion of the cyclopeptide toxin.

Thioctic Acid

During the past ten years, the use of thioctic acid (alpha lipoic acid) in the successful treatment of A. phalloides-type mushroom poisoning has been reported enthusiastically in the European literature.[15,18,22,23] Finestone and co-workers reported the first successful treatment of A. phalloides-type mushroom poisoning with thioctic acid in the United States in 1968.[24,25] In their patient, eight days after ingestion of A. verna, 300 mg of thioctic acid was infused intravenously over 24 hours for three days. After 72 hours, the dosage was tapered over six days and discontinued when the serum transaminase levels returned to normal.

Since 1968, thioctic acid has been used experimentally in the United States in 11 other patients with A. phalloides-type poisoning. A review of these cases shows that in nearly all there was chemical and clinical evidence of hepatocellular damage; ten of the patients recovered without major sequelae (Table 3).

The only side effect of thioctic acid to date has been hypoglycemia. Whether the hypoglycemia was a direct effect of the drug[26,27] or a result of severe hepatic damage[2] secondary to mushroom poisoning remains unclear. To date, the only patient in the United States who did not respond favorably to thioctic acid as far as we know received the drug late in the course,[28] since the patients in all other reports survived when given the drug two to three days after ingestion (except that of Finestone and co-workers[25]). This indicates that early administration may be necessary for the drug to produce its effect.

Results of studies of thioctic acid use in animals in which toxic effects were induced with amanitin are varied. In two studies, administration of thioctic acid failed to reverse the toxic effects[20,26] and in one[26] hypoglycemia occurred. The significance of the hypoglycemia observed in man and animals and the reported lack of effectiveness of thioctic acid in animals need to be studied further.

The investigational drug protocol approved by the Food and Drug Administration for the use of thioctic acid states that it should be used only in known or strongly suspected cases of ingestion of A. phalloides, A. virosa or A. verna mushrooms.[29] Although they are not included in the protocol, G. autumnalis, marginata and venenata contain amanitin, and thioctic acid is appropriate treatment (Table 3) in poisonings by these mushrooms as well.

Initially, 25 mg of thioctic acid in a solution of glucose and water may be infused intravenously four times a day. On the second day, depending on clinical status, the dose may be increased to 75 mg four times a day. This may be continued

for 14 days using findings on daily liver enzyme function tests as a guide. Measurement of serum glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), creatinine, blood urea nitrogen and glucose levels and urinalysis should be carried out at least once a day and more frequently if necessary. Because thioctic acid is sensitive to light and heat, bottles and infusion lines containing the solution must be covered.

The mechanism of action of thioctic acid in patients with A. phalloides-type poisoning is unclear. Lipoic acid is a component of coenzymes necessary to oxidize ketoacids such as pyruvate. It has been suggested that (1) thioctic acid may produce its protective effect at the level of the enzymes of the Krebs cycle[29] or (2) that the disulfide constituents of thioctic acid form a complex with the cyclopeptides to modify their toxicity.[20,29]

Because of the high morbidity and mortality of A. phalloides-type poisoning, it would seem impossible to conduct a random double-blind clinical study of thioctic acid. While the cases represented here and the three in which we consulted cannot offer unequivocal evidence that thioctic acid was useful, they do show that the agent is safe to administer and apparently contributed to the recovery of these patients despite clinical and chemical evidence of severe liver impairment before it was given (Table 3). However, the contribution of intense supportive care is difficult to assess.

Since the chromatographic assay method now enables specific and definitive diagnosis of A. phalloides-type mushroom poisoning and since thioctic acid lacks significant toxicity, we believe that the use of thioctic acid concomitantly with vigorous supportive treatment in such cases is justified. Except for the occurrence of hypoglycemia, this agent appears to be safe when used properly. Despite the much larger initial dose given in Case 1 and the reported use of this drug for over 13 days in another (Table 3, Case No. 8), no ill effects have been observed. In Case 2, a seven day course of thioctic acid was administered according to the protocol, and the response was impressive.

Reports of Cases

Case 1. A 32-year-old man had been well until March 2, 1973 when nausea, vomiting, fever and severe diarrhea developed 12 hours after he had eaten four large wild mushrooms picked in Fresno County, California. The family physician administered atropine and prochlorperazine, but the nausea and vomiting persisted. The patient was admitted to a local hospital with severe dehydration and oliguria. Laboratory data included SGOT, 2,580; SGPT, 4,420 units per ml; total bilirubin, 1.9 (direct, 1.3 and indirect, 0.6); blood urea nitrogen, 41, and creatinine, 1.9 mg per 100 ml.

The patient was transferred to the University of California Moffitt Hospital in San Francisco, where symptoms of severe hepatic injury continued, although renal function returned toward normal values. Because of strong suspicion that the mushrooms ingested by the patient were A. phalloides-type (subsequently confirmed by chromatographic detection of alpha- and gamma-amanitins and phalloidin at the Toxicology Laboratory of San Francisco General Hospital) informed consent was obtained from the patient to administer thioctic acid.

A total of 300 mg per 24 hours in 10 percent glucose in H_2O were infused intravenously on day three after ingestion. The patient's condition improved and there was resolution of symptoms. By the sixth day of thioctic acid administration, the following values were noted: total bilirubin, 0.8 mg per 100 ml; direct bilirubin, 0.3 mg per 100 ml; SGOT, 40 units, and SGPT, 250 units per ml. Thioctic acid therapy was terminated and the patient was discharged.

Case 2. An 87-year-old man had been in good health until December 16, 1974 when severe nausea, vomiting, profuse diarrhea, and cramping pain of the arms, lower abdomen and legs developed suddenly; he was admitted to a local hospital. The patient 22 hours before had eaten approximately a half cup of mushrooms collected in Santa Clara County. There was no excessive salivation, lacrimation, photophobia or diplopia but the patient was confused and disoriented. He became progressively oliguric and was transferred to the University of California Moffitt Hospital in San Francisco.

On admission, the patient was alert and oriented, but anorectic, nauseated and vomiting occasionally. Prothrombin time was 15.4 seconds (control 11.4) and partial thromboplastin time was 43.7 seconds (control 28.6). The serum creatinine level was 4.4, glucose level was 208 and blood urea nitrogen value was 43 mg per 100 ml. Cooked and uncooked specimens of mush-

rooms collected by the patient were obtained for chromatographic analysis (also done at San Francisco General Hospital's Toxicology Laboratory) and found to contain amanitin and phalloidin.

Treatment with thioctic acid, 25 mg every six hours infused intravenously in 10 percent glucose in H_2O or saline solution, and neomycin, 1 gram per day given orally, was started on day three after ingestion. After 24 hours, the dosage of thioctic acid was increased to 75 mg every six hours. On day two of thioctic acid therapy, levels of blood urea nitrogen decreased to 39 and creatinine to 2.1 mg per 100 ml. The following clinical values were noted: SGOT, 2,160; SGPT, 1,350; LDH, 4,640; alkaline phosphatase, 65 units per ml, bilirubin, 2.3 mg per 100 ml, and prothrombin time, 18.4 seconds (control 11.3). On day seven of thioctic acid therapy, administration of the drug was discontinued because liver function tests had returned to normal values.

On December 23, blood urea nitrogen and serum creatinine levels were 73 and 14.8 mg per 100 ml, respectively; hemodialysis was begun. On December 30, findings on liver function tests had returned to within normal limits except for slight hypoalbuminemia and an elevated alkaline phosphatase level. Dialysis was carried out on three subsequent occasions (January 2, 6 and 10). On January 23, 1975, renal function was stable, with blood urea nitrogen levels varying between 100 and 110 and serum creatinine levels between 7 and 8 mg per 100 ml, and except for a persistently elevated alkaline phosphatase level, findings on liver function tests had returned to the normal range and gastrointestinal bleeding, atrial fibrillation, and pericardial and pleural effusions had successfully resolved; the patient was discharged.

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Medical
PROGRESS

Refer to: Morris JF: Spirometry in the evaluation of pulmonary function (Medical Progress). West J Med 125:110-118, Aug 1976

Spirometry in the Evaluation of Pulmonary Function

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Spirometry should be more widely used in routine examinations. Equipment should meet the individual physician's or hospital's needs and include either a dependable water-sealed spirometer or an easily calibrated and accurate electronic spirometer. Justifiable concern over the reliability of electronic spirometers has resulted in requests to determine performance standards for these medical devices. Predicted normal standards must apply to the particular spirometer. Recommended tests are those of vital capacity (VC), forced vital capacity (FVC), one-second forced expiratory volume (FEV_1), the ratio of one-second forced expiratory flow (FEF200-1200) and forced midexpiratory flow (FEF25-75 percent). The maximum voluntary ventilation (MVV) test may be useful for evaluation of work disability and detection of extrathoracic obstruction. Additional consideration may be given to measurements of total lung capacity (TLC) to discriminate between restrictive and obstructive impairment and the forced end-expiratory flow (FEF75-85 percent) to detect mild small airway obstruction. At this time, flow-volume curves measurement cannot be justified for routine clinical use.

THE INCREASING PREVALENCE of chronic respiratory disease, particularly chronic bronchitis and emphysema (COPD), is reflected in growing concern regarding its diagnosis and control. The dimensions of the problem of chronic respiratory disease are inexactly known. Estimates of at least 12 million Americans afflicted with some degree of COPD have been offered but the true figure is probably several-fold greater. The dollar costs of COPD are impressive. It ranks behind arteriosclerotic heart disease and arthritis as a cause of early disability payments under the Social Security Administration. The National Center for Health Statistics has tabulated that for 1973 there were 41,042 deaths due to COPD. A steep upward trend in mortality from COPD is reflected in the increase in the death rate attributed to chronic bronchitis, emphysema and asthma from 5.0 per 100,000 population in 1950 to 19.6 in 1973. The exact slope is difficult to measure because of changes in diagnostic terminology. Since 1968, the Health

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ABBREVIATIONS USED IN TEXT

COPD = chronic bronchitis and emphysema
FEF25-75 percent = forced midexpiratory flow
FEF75-85 percent = forced end-expiratory flow
FEF200-1200 = ratio of one-second forced expiratory flow
FEV_1 = one-second forced expiratory volume
FRC = functional residual capacity
FVC = forced vital capacity
MVV = maximum voluntary ventilation
RV = residual volume
TLC = total lung capacity
VC = vital capacity

Resources Administration has combined chronic obstructive lung disease with emphysema, bronchitis and asthma as a cause of death. It is estimated that COPD utilizes approximately 15 percent of both physicians' time and hospital facilities in the United States.

A priority need is detection of COPD by primary physicians at an early stage. This requires reliable yet simple and relatively inexpensive techniques, both to detect early dysfunction and to document the extent of established pulmonary disease. Spirometry is the basic essential for practicing physicians.

Background

The determination of lung volumes began in 1800 with the measurement of residual volume by Davy using a hydrogen gas dilution technique. The practical origin, however, dates from the impressive work of the Reverend John Hutchinson in 1844.[1] He not only designed the first spirometer but also designated the expiratory vital capacity and developed normal standards based upon approximately 2,000 assorted English persons. He recognized the positive correlation with height and the negative relationship with age, excessive weight and pulmonary diseases. Dynamic lung volume measurements were delayed for a century until the valuable studies at Bellevue Hospital by Cournand, Richards and their colleagues in the 1940's.[2] Additional contributions to the measurement of timed vital capacity came from Tiffeneau and Pinelli in 1947[3] and Gaensler in 1951.[4] Tiffeneau and associates in 1949 first advocated the use of the one-second forced expiratory volume/forced vital capacity (FEV_1/FVC) ratio.[5] Leuallen and Fowler contributed the maximum midexpiratory flow test in 1955.[6]

Nomenclature has been troublesome and remains so today. Gandevia and Hugh-Jones in 1957 published widely accepted terminology for pulmonary physiology.[7] The Committee on Pulmonary Physiology of the American College of Chest Physicians in 1963 offered their modification of the terminology of dynamic lung volumes.[8] In 1975, a joint committee of the American College of Chest Physicians and the American Thoracic Society published a broad exposition on pulmonary nomenclature.[9] This latest effort may rescue us from the present welter of abbreviations and terms.

Physiologic Determinants of Spirometry

Forces are necessary to overcome the three opposing pulmonary forces of *inertia* and *compliance* of the lung and chest wall, and *resistance* to air flow and tissue motion. The interaction of these forces generates the measures of pressure, flow and volume. Lung volumes are influenced by degrees of inspiratory and expiratory pressures and by age, height and sex. Body position is also important. For example, changing from the standing to the supine position reduces vital capacity, functional residual capacity and total lung capacity. This is usually explained by an upward shift of the diaphragm, changes in the chest wall dimensions and increase in thoracic blood volume. Diseases that restrict lung volumes encompass a wide collection of pathologic entities including those affecting the chest wall, lung interstitium and pulmonary vasculature, reduction of lung volume by surgical procedures or thoracic space-occupying lesions, and by abdominal distention. All these entities are characterized by a reduced total lung capacity.

Flows are largely dependent upon respiratory muscular effort, force of elastic recoil and the diameter of the airways. The initial forced expiratory effort achieves a peak flow extremely rapidly, normally within the first 100 milliseconds and is dependent upon muscular effort. The flow decreases steadily with decreasing lung volume, is determined by the lung elastic recoil and the patency of the airways, and is largely independent of muscular effort. Pathologic processes which reduce elastic recoil or increase obstruction to air flow impair forced expiratory flows.

TABLE 1.—*Respiratory Health Questionnaire*

1. Do you usually cough or have to clear your throat in the morning or when getting up?
2. Do you usually cough for as many as three months each year?
3. Do you usually bring up any mucus, sputum or phlegm from your chest during the day?
4. Do you usually bring up any mucus, sputum or phlegm for as many as three months each year?
5. Do you have to stop for breath when walking at your own pace on level ground?
6. Do you get short of breath when walking with other people of your own age on level ground?
7. Do you ever wheeze?

Indications for Spirometry

Pulmonary function testing is indicated for all persons in whom there are symptoms and a positive response to a suitable respiratory questionnaire (Table 1).[10] It should be especially indicated for persons with complaint of shortness of breath. In any person, particularly cigarette smokers or asthmatics, spirometry will provide a baseline performance value for comparison with results of future tests. The impact of air pollution on nonsmokers may be detected by such comparison. Specific indications for ventilatory function testing include the following:

- To measure the extent of pulmonary function impairment.
- To help determine the type of impairment, such as restrictive, obstructive or a combination.
- To study possible effectiveness of bronchodilator therapy and the degree of air obstruction reversibility.
- For preoperative evaluation, especially for surgical procedures on the chest or upper abdomen.
- To follow the course of a patient's disease.
- To establish baseline ventilatory function.

Equipment

The traditional spirometer has been the water-sealed apparatus used in previous studies to obtain normal standards for ventilatory function. Minor nuisances are water spillage if moved and the need for maintaining proper water level. Waterless spirometers such as the bellows are less expensive but sacrifice accuracy for portability. With the rapid development of biomedical engineering, electronic spirometers have appeared which offer rapid readings, memory capability, digital displays and computer-assisted readouts. Associated with these devices are problems of accuracy, reliability and applicability of normal standards obtained from water-sealed spirometers.[11,12] The increasing need for screening large numbers of patients and the problem of high labor costs may result in the displacement of nonelectronic spirometers by either electronic ones or nonelectronic ones coupled to electronic accessories, permitting rapid measurement and data processing. Additional studies are needed to assess the suitability of these devices. Of particular concern is the inclusion of tests of questionable value. Physicians should cautiously approach the acquisition of a spirometer or other device for pulmonary function testing by answering some important questions first:

- What tests will be of value in my practice?
- How many tests will be made daily or weekly?
- What normal standards are available?
- What is the requirement for instrument calibration and can it be done in the field?
- Is efficient service available in my area?
- Is the equipment versatile or can it be expanded for other studies?
- What recording system is available for a permanent record?
- What are the initial and the maintenance expenses?

The electronic devices available for ventilatory function testing are valuable for rapid testing of a larger number of subjects with uniform accuracy. Instead of a bellows or water-sealed bell, they use hot wire anemometers, thermistors, thermocouples, pneumotachographs or turbines to detect flow and electronically calculate volumes. They can measure, calculate, display and print out results, some including percentage of predicted normal values in a fraction of the time required by previous apparatus. The capability of providing memory function and calculation of percentage of predicted normal values increases the complexity and cost of the equipment, but does widen the spectrum of testing and reduces manual handling of the data. Before being seduced by the claims of the capacity of greater number of tests, digital displays, rapidity and ease of calculation, physicians should be certain that the qualities of reliability and consistency possessed by the water-sealed and rolling seal spirometers are not being sacrificed. If only a limited number of tests are done, such as up to six per day, a water-sealed or rolling seal spirometer is advisable. Ideally, the addition of electronic data calculation and display increases the usefulness of spirometry. Conver-

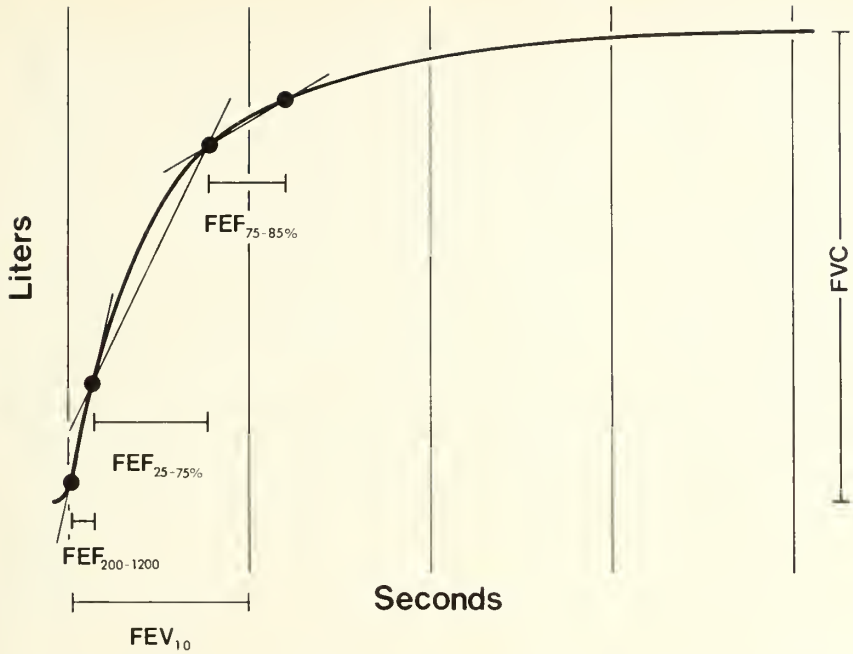


Figure 1.—Components of the forced expiratory vital capacity curve.

sion of the data obtained at ambient conditions of temperature, barometric pressure and water vapor saturation to body conditions is desirable. A final essential ingredient is a capable, trained assistant who is able to get maximal efforts in a humane manner from a patient and to maintain the equipment properly.

Spirometric Tests and Interpretation

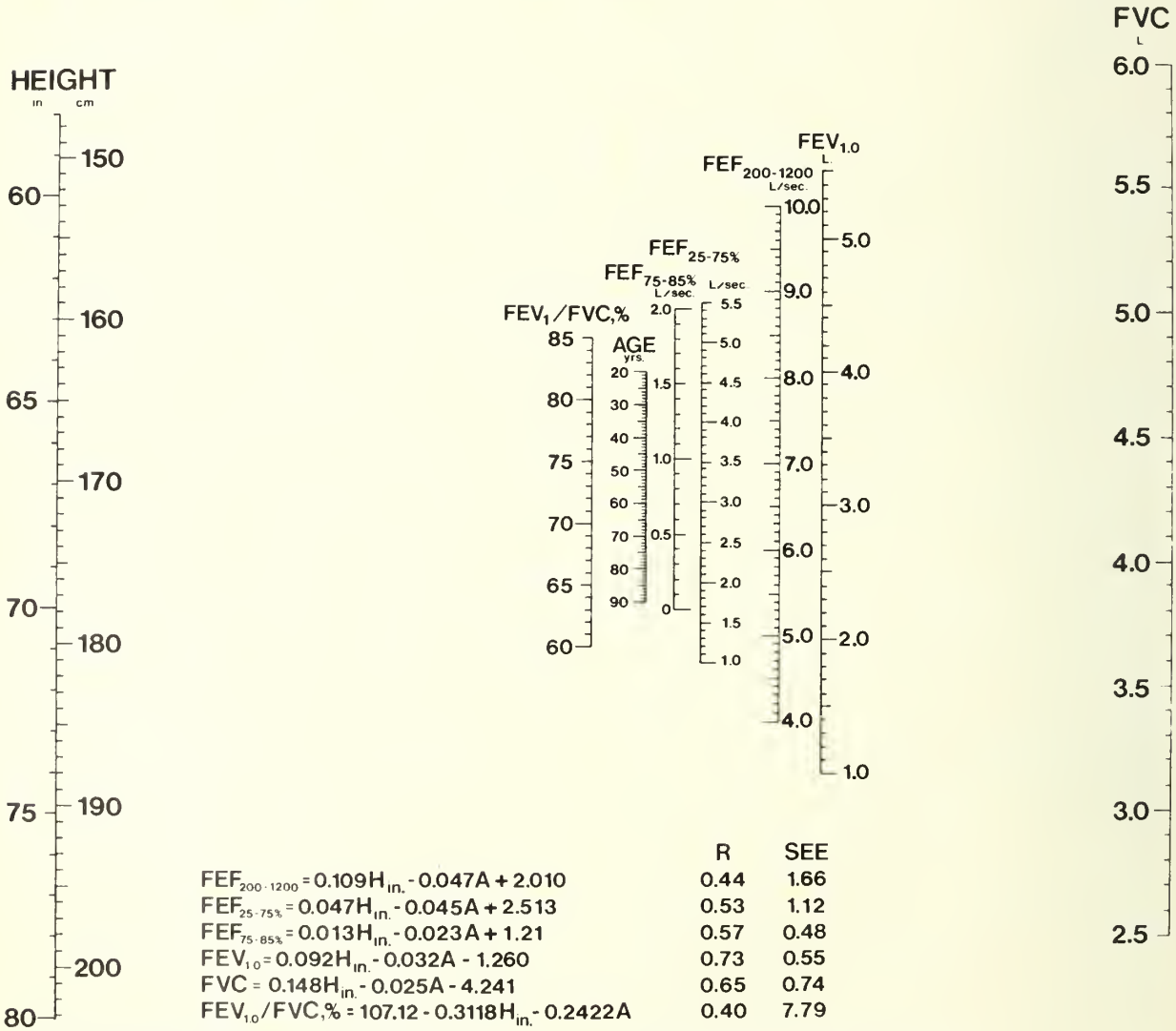
The principal use of spirometry is to record vital capacity (VC) and, more important, to record forced expiratory flow measurements. Both the vital capacity and forced vital capacity (FVC) studies should be done. The VC is the maximum volume of air exhaled from the point of maximum inspiration. The FVC differs only by using a maximally forced expiratory effort. In simpler terms, the VC is slow and the FVC fast. Ordinarily, their findings are similar and any significant discrepancy suggests air trapping. The test for vital capacity is useful primarily as an index of lung restriction but is also an indirect reflection of lung or chest wall compliance. A variety of other spirometric tests may be carried out but some are less useful either because of effort-dependency or lack of reliable normal standards. Included in this category are tests for peak flow and forced expiratory volumes in 0.5, 2 or 3 seconds. Forced expiratory vital capacity is measured against time. The measurements of flow depend indirectly on the resistance to expired air flow. Of special importance is the site of obstruction to air flow. It has been suggested that both by pathological examination and physiological testing, the initial site of involvement in COPD is the small airways less than 2 mm in diameter.[13,14] Because 10 to 15 percent of total airway resistance is provided by the large total cross-sectional area of these small airways, most pulmonary function tests are too insensitive to reflect this relatively small contribution to the total. As the disease process progresses, larger airways become involved. Figure 1 indicates the flow measurements in different portions of the FVC curve. By partitioning the components of the FVC curve, it may be possible to locate the primary areas of dysfunction.

The FEV_1 as seen in Figure 1 occupies approximately the first 75 to 80 percent of the FVC in normal adults. With increasing airway obstruction, the FEV_1 forms a decreasing percentage of the FVC. The FEV_1 appears to be relatively less sensitive in detecting small airway disease than the forced midexpiratory and end-expiratory flows. Controversy exists as to the measurement of zero time. The basic choice is whether to place it at the intersection of the FVC curve and the exhaled 200 ml volume line[15] or to extrapolate the steepest part of the FVC curve back to the exhaled zero volume line.[16]

The ratio of the FEV_1 to FVC may permit a rough distinction between restrictive, obstructive or a combination of both.[17] A normal FEV_1/FVC percent does not rule out small airway obstruction, which is better indicated by the forced mid-

expiratory or end-expiratory flows. The FEV_1/VC percent is preferable to the FEV_1/FVC percent for distinguishing between restrictive and obstructive impairment because of the reduction of the FVC by the air trapping related to obstructive airway disease.

The FEF200-1200 or maximum expiratory flow involves approximately the first 25 percent of the FVC in a normal adult. This is believed to be the effort-dependent portion and subject to variability. The peak flow also falls in this portion and suffers from this fault as well as its questionable functional importance as an unsustained flow. Both these tests may reflect abnormalities in the large airways or the larynx. The test of FEF25-75 percent or maximum midexpiratory flow has been available for 20 years and recently its value for early detection of small airways obstruction has been suggested.[18] Because the test reflects air flow in distal airways and is considered to be effort-independent, it has been preferred to the previously mentioned tests for the measurement of obstructive pulmonary disease. To increase the sensitivity to impairment of air flow in small airways, the forced end-expiratory flow (FEF75-85 percent) has been recently introduced. Our laboratory found the test to be more discriminatory than the FEF25-75 percent in distinguishing between male smokers and nonsmokers 30 to 49 years of age if 75 percent of predicted normal mean values was used to separate normal from abnormal.[19] It should be noted that premature termination of the



	R	SEE
$FEF_{200\text{-}1200} = 0.109H_{in.} - 0.047A + 2.010$	0.44	1.66
$FEF_{25\text{-}75\%} = 0.047H_{in.} - 0.045A + 2.513$	0.53	1.12
$FEF_{75\text{-}85\%} = 0.013H_{in.} - 0.023A + 1.21$	0.57	0.48
$FEV_{1.0} = 0.092H_{in.} - 0.032A - 1.260$	0.73	0.55
$FVC = 0.148H_{in.} - 0.025A - 4.241$	0.65	0.74
$FEV_{1.0}/FVC,\% = 107.12 - 0.3118H_{in.} - 0.2422A$	0.40	7.79

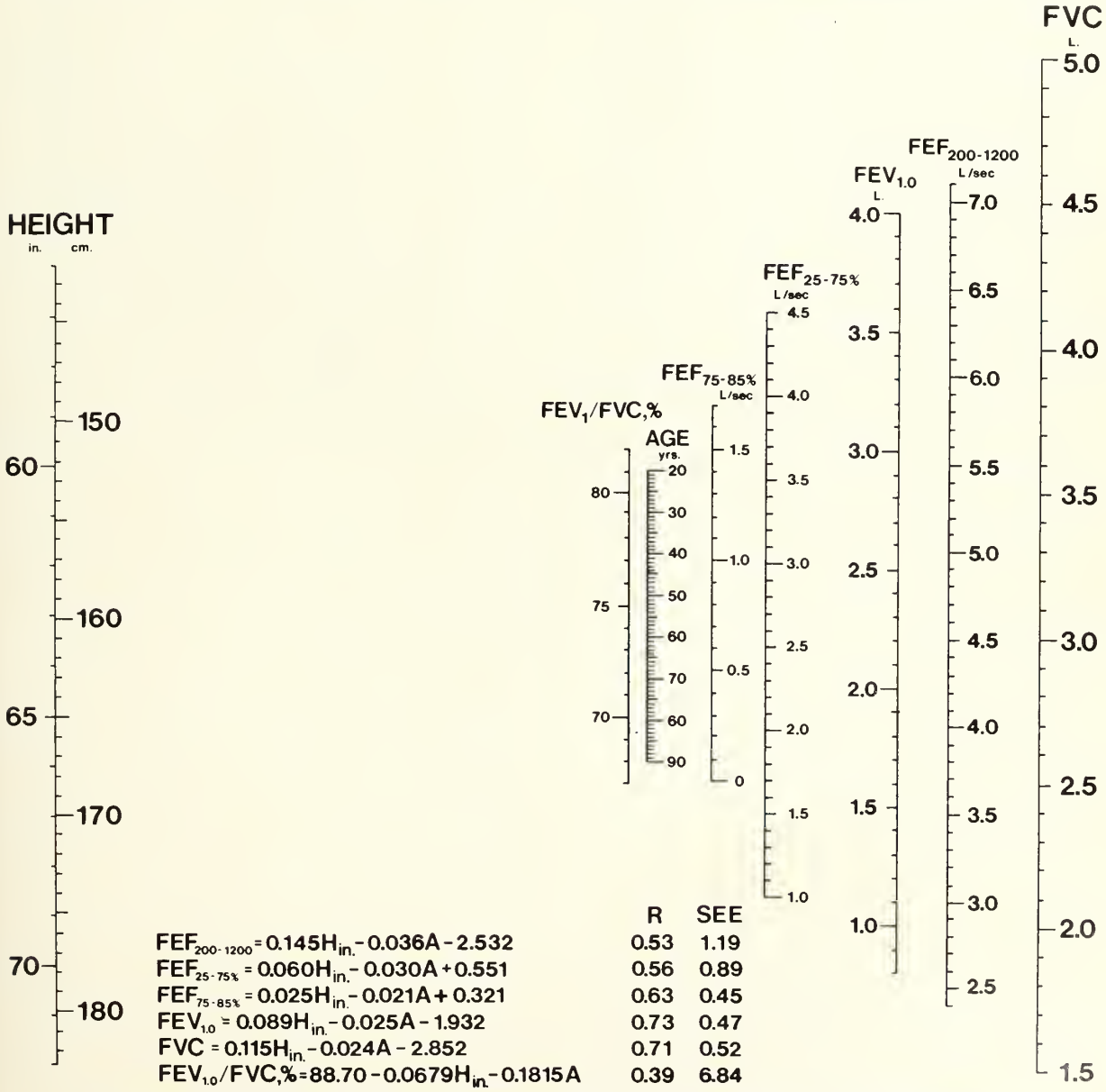
BTPS = body temperature, ambient pressure, saturated with water
FEF200-1200 = ratio of one-second forced expiratory flow
FEF25-75% = forced midexpiratory flow
FEF75-85% = forced end-expiratory flow
FEV_1 = one-second forced expiratory volume
FVC = forced vital capacity

Figure 2.—Prediction nomogram for normal men (BTPS).

FVC maneuver will cause serious errors in measurement, especially of the FEF25-75 percent and FEF75-85 percent.

To estimate the degree of reversible airway obstruction, aerosolized bronchodilator solutions may be administered. Ideally, the patient should not have had any type of bronchodilator drug for at least 12 hours before the test. When the spirometric tests are repeated five to ten minutes after inhalation of the bronchodilator aerosol, improvement greater than 20 percent may be considered significant. Failure to achieve this improvement, however, does not rule out possible benefit from a therapeutic trial of oral or aerosolized drugs.

The test of maximum voluntary ventilation (MVV) is a sustained exertional maneuver reflecting both thoracic and extrathoracic components. It has proved useful in evaluating work disability and exertional dyspnea. The patient is asked to breathe as rapidly as possible for 12 to 15 seconds using a depth of inhalation greater than his resting tidal volume. In carrying out this test, three pulmonary variables come into play, namely, amplitude of the tidal volume, frequency of breathing and the degree of lung inflation. Optimum frequency has been reported to vary between 70 and 110 breaths per minute. Because of



	R	SEE
$FEF_{200-1200} = 0.145H_{in.} - 0.036A - 2.532$	0.53	1.19
$FEF_{25-75\%} = 0.060H_{in.} - 0.030A + 0.551$	0.56	0.89
$FEF_{75-85\%} = 0.025H_{in.} - 0.021A + 0.321$	0.63	0.45
$FEV_{1.0} = 0.089H_{in.} - 0.025A - 1.932$	0.73	0.47
$FVC = 0.115H_{in.} - 0.024A - 2.852$	0.71	0.52
$FEV_{1.0}/FVC,\% = 88.70 - 0.0679H_{in.} - 0.1815A$	0.39	6.84

Figure 3.—Prediction nomogram for normal women (BTPS), see Figure 2 for abbreviations.

TABLE 2.—*Categories of Ventilatory Impairment*

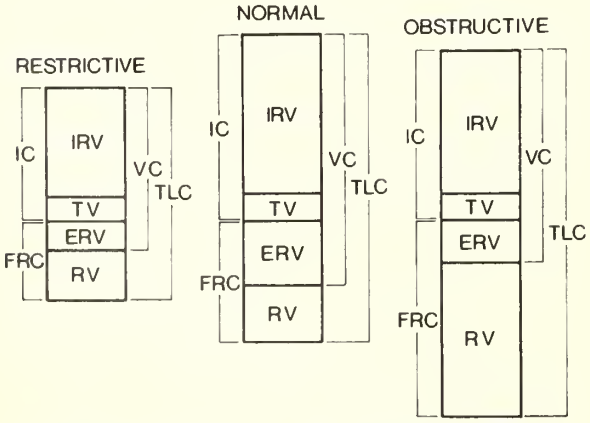
	VC, FVC, FEV_1, MVV	*FEF200-1200, FEF 25-75%, FEF75-85%*
Normal	>80*	>75
Mild	65 - 80	60 - 75
Moderate	50 - 64	45 - 59
Severe	35 - 49	30 - 44
Very severe	<35	<30

*Percent of predicted normal
VC = vital capacity
FVC = forced vital capacity
FEV_1 = one-second forced expiratory volume
MVV = maximum voluntary ventilation
FEF200-1200 = ratio of one-second forced expiratory flow
FEF25-75% = forced midexpiratory flow
FEF75-85% = forced end-expiratory flow

the variables, it is not possible to know if a truly maximum ventilation has taken place. It is an exhausting test requiring a truly maximum effort. Various prediction formulas have been suggested, frequently based on a multiple of the timed vital capacity, a practice which has been justifiably criticized.[20] A rough guide for a maximum effort is the agreement between the percentages of the predicted normals for the FEV_1 and the MVV. Because the MVV involves both inspiratory and expiratory phases, obstruction in the larynx or trachea may preferentially reduce inspiratory flow.[21] This may result in a discrepancy between the percentages of the predicted FEV_1 and MVV despite maximal efforts. Predicted normal standards have been provided but the wide variations should be noted.[15,22] Techniques of measurement of all these ventilatory function tests have been previously described.[15,19]

Interpretation remains the least precise aspect of pulmonary function testing. Of first order is the need for useful normal standards. Figures 2 and 3 show nomograms developed in the author's laboratory based upon spirometric tests of healthy adult nonsmokers,[17,19,23] but it is unlikely that any single set of normal standards can be universally applied. Significant variables affecting the standards for ventilatory function include age, height, sex, size of the sample tested, racial and ethnic composition, criteria for normality, tobacco smoking, environmental conditions, altitude of residence, apparatus and techniques. Regardless of the normal mean values obtained, a distribution curve will result and the range of normality must be established. The sensitivity of the test will be influenced by selection of the extent of deviation from the predicted mean value separating normal from the abnormal subject. Ideally, a multiple of the standard error of estimate such as 1.65 standard errors of estimate which excludes 5 percent of normal persons with lesser values should be used. Alternately, a percentage of the predicted mean value can be used. This is the simplest and most commonly employed method.[24] Table 2 shows a classification of ventilatory impairment to be used with spirometric tests. The flow rates have wider variations from the mean values than the other tests. Prediction standards for normal children of 4 to 18 years old have been reported by Weng and Levison.[25]

It is popular to classify types of ventilatory impairment as restrictive, obstructive or a combination of both. Usually, reduction of vital capacity indicates restrictive impairment. With severe obstructive pulmonary disease, the vital capacity may be reduced due to airway closure. Distinction may be made by measurement of functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC). As shown in Figure 4, obstructive impairment is characterized by increased TLC, FRC and RV with a normal or reduced VC. Restrictive impairment consistently has a reduced VC and TLC with a normal or reduced FRC and RV. Measurement of FRC requires additional equipment and involves either a closed circuit helium or nitrogen equilibration technique or an open circuit nitrogen washout.[26] If TLC is not calculated, the flow diagram in Figure 5 may be of value in determining the type of ventilatory impairment. The use of Table 2 will provide the added dimension of the degree of impairment. This system can be adapted for automated in-



IC Inspiratory Capacity
FRC Functional Residual Capacity
VC Vital Capacity
TLC Total Lung Capacity
IRV Inspiratory Reserve Volume
TV Tidal Volume
ERV Expiratory Reserve Volume
RV Residual Volume

Figure 4.—Diagram of lung volumes and capacities in normals and patients with restrictive and obstructive pulmonary diseases.

terpretation by a calculator that can be programmed or a computer.

Serial testing of a patient will be of greater value than comparing him or her with a sample group but many patients are seen only after some degree of impairment has occurred. Incorporation of routine spirometry into the periodic examinations of cigarette smokers or any persons with pulmonary symptoms cannot be too strongly advocated.

The expiratory flow-volume curve was introduced by Hyatt and co-workers in 1958.[27] Claims for advantages over volume-time curves of conventional spirometry include better visualization of the reduction of flow at specific volumes. Plotting maximum expired flow against volume provides useful information regarding obstructive and restrictive ventilatory impairment but it represents only a first order derivative of the forced expiratory flow. Its disadvantages include the requirement for simultaneous recording of two variables, usually on an X-Y recorder or storage oscilloscope, and the lack of applicable normal standards. Although useful in clinical research and the teaching of lung mechanics, it is doubtful if the flow-volume curve provides additional useful clinical information not provided by spirometry.

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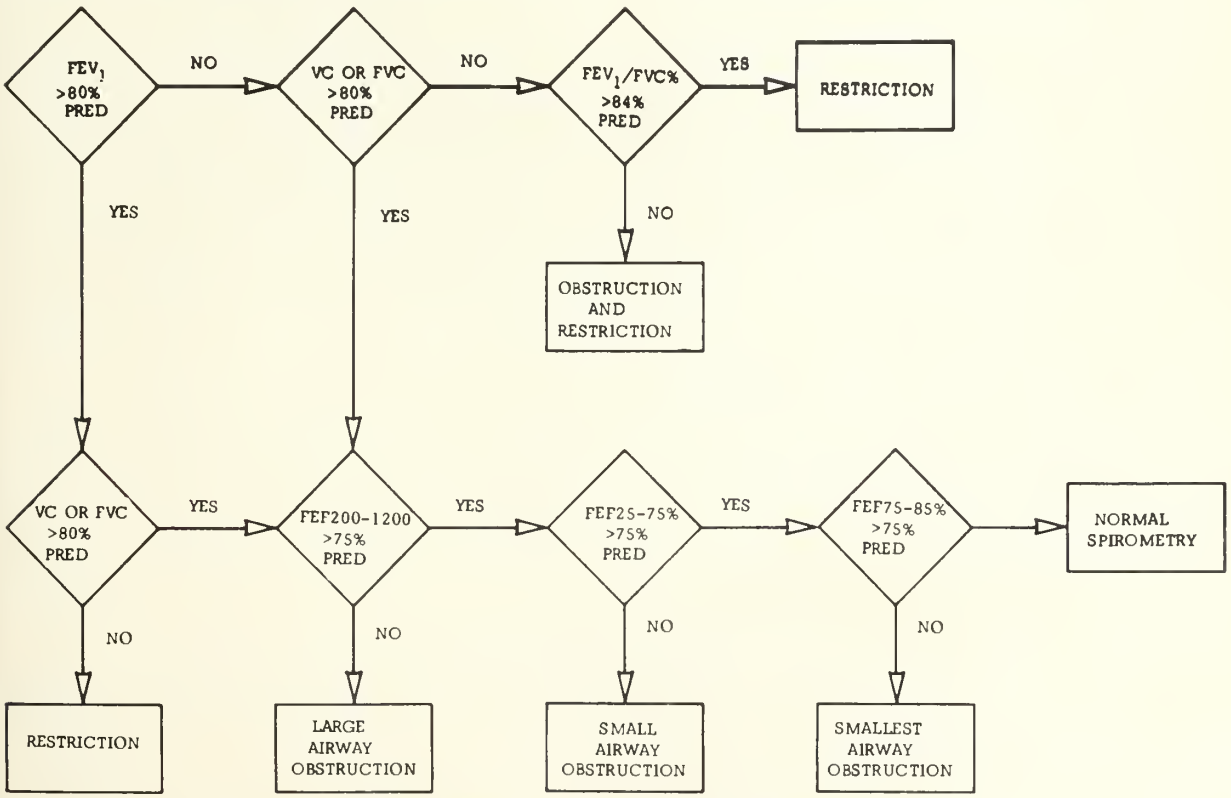

VC = vital capacity See Figure 2 for other abbreviations

Figure 5.—Flow diagram for interpretation of spirometric data.

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Errors in Blood Pressure Determination

. . . We may actually get false blood pressure readings (when taking them) and the first and most obvious cause is bad equipment. You have to have your equipment standardized and checked out every year, whether it is an aneroid or mercury sphygmomanometer. You should not bring the patient running into your office, have him sit down and roll up his sleeve and take his blood pressure. Talk to him for awhile so that there is at least five minutes of inactivity and peace. The antecubital fossa should be at the heart level in the sitting position when you take the blood pressure. If it is much higher, the blood pressure will be lower. If the arm is low in relation to the heart, the blood pressure will be higher. You certainly do not want to start in the auscultatory gap with your systolic blood pressure, so if there is any doubt where you are, feel the radial pulse. . . . An obese arm is a particular problem and I want to emphasize this. In women heavier than 200 pounds and in men heavier than perhaps 250 pounds, I do not think we often see a very reliable blood pressure utilizing a standard cuff. There are two things that you can do. One is to use your standard cuff on the forearm and listen over the radial artery. This is pretty good for systolic but I do not often hear very well the diastolic blood pressures by this technique. I think for any of you who are seeing a large hypertensive population or a lot of very heavy patients, you should get a thigh cuff, because I think you will be amazed at the difference in blood pressure readings between the two cuff sizes in very heavy arms.

Obstruction in a proximal artery may give a falsely low blood pressure on the involved side, so you should either take blood pressure readings in both arms or, more easily, feel the radial pulses for similar amplitude. And finally, there is an occasional patient, and this is more apt to occur in a diabetic patient, whose brachial artery is very rigid and calcified and it cannot be compressed. On the other hand, you will occasionally take a blood pressure measurement and not get any diastolic pressure at all; it will go all the way down to zero. Now, I do not know what that means.

—NEIL W. SWINTON, JR, MD, *Boston*

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Specialty Conference

Moderator
PHYLLIS A. OILL, MD

Discussants
ARNOLD S. BAYER, MD
J. MICHAEL CRILEY, MD
ARNOLD H. BLAUFUSS, MD
LARRY FISHER, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Refer to: Oill PA, Bayer AS, Criley JM, et al: Infectious disease emergencies—Part II: Patients presenting with cardiac decompensation or circulatory insufficiency (shock), *In* Infectious disease emergencies—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conference). West J Med 125:119-136, Aug 1976

Infectious Disease Emergencies

PART II:

Patients Presenting with Cardiac Decompensation or Circulatory Insufficiency (Shock)

PHYLLIS OILL, MD:* The second part of the symposium on infectious disease emergencies focuses on patients who present to an emergency department with cardiac decompensation or circulatory insufficiency (shock). Although there are numerous infectious processes that can cause this type of clinical presentation (see Table II-1), in this section we will review those diseases that affect the cardiovascular system primarily.

Dr. Arnold Bayer will now begin the discussion by reviewing the clinical and laboratory aspects of infective endocarditis. Drs. Criley and Blaufuss will then discuss the cardiac and hemodynamic manifestations of this disease process.

ARNOLD S. BAYER, MD:† Cardiac infections remain one of the most difficult problems, both diagnostically and therapeutically, for clinicians to cope with. The consequences of delayed recognition and treatment of these disorders are indeed life-threatening. There, perhaps, is nothing so challenging to a medical staff as a patient with acute deterioration of cardiac function caused by an infectious process. Such a situation not only calls upon a physician to treat the manifest cardiac failure, but also to recognize and manage the underlying infectious process with prompt and appropriate therapy; in addition, one must know when early surgical intervention is called for.

In this section of the symposium, emphasis will be placed on the most important aspects of the evaluation and management of infective endocarditis and pericarditis. Additionally, the various causes of infectious myocarditis will be mentioned briefly.

Infective Endocarditis

Some general comments should be emphasized about infective endocarditis. In the past 20 to 25 years, there has been a pronounced increase in the average age of patients with endocarditis, with over 50 percent now being above age 50.[1] Also, in 40 percent of such patients there is neither a history nor clinical or autopsy evidence of antecedent cardiac disease.[1] The classification of endocarditis into acute and subacute forms tells one nothing more than the clinical course of the infection. It is now apparent that any organism can cause an acute, fulminant type of infection or, alternatively, more indolent, subacute clinical features.[2]

Fever is still the most common sign in infective

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacillus
DIC = disseminated intravascular coagulation
RHD = rheumatic heart disease

endocarditis, occurring in 90 to 95 percent of cases.[1,3] However, it must be remembered that fever can be minimal or absent in older patients, patients with renal or cardiac failure or in persons who have received antibiotic therapy previously.[1]

In the acute form of endocarditis, especially with rightsided involvement, cardiac murmurs may be minimal or absent.[4] Additionally, it is often difficult to appreciate changing murmurs. However, if there is a distinct alteration in the quality or intensity of a murmur, this usually heralds substantial architectural damage to the infected valve.[5] Of equal importance in this clinical situation is that the classical peripheral signs of endocarditis—such as Osler's nodes, Janeway lesions, Roth spots, splenomegaly and the like—are often absent.[1] Although these signs are important to look for and significant if found, their absence should not dissuade one from the diagnosis of infective endocarditis.

TABLE II-1.—*Infectious Diseases Presenting with Cardiac Decompensation or Circulatory Insufficiency (Shock)*

Cardiac Infections
- Endocarditis
- Pericarditis
- Myocarditis

Mediastinitis*
Septic shock or febrile hypotension
- Gram-negative organisms
- Gram-positive organisms
- malaria especially falciparum

Disseminated intravascular coagulation (DIC) secondary to infection
Pneumonia with severe hypoxia†
Infectious diarrheal syndromes—particularly staphylococcal enteritis, cholera, fulminant amebic colitis*
Peritonitis*
Anaphylaxis secondary to antibiotic therapy†

*Will be discussed in Infectious Disease Emergencies, part IV: Patients presenting with gastrointestinal disorders.
†Will be discussed in Infectious Disease Emergencies, part III: Patients presenting with respiratory distress syndromes.

TABLE II-2.—*Infective Endocarditis—Less Common Clinical Presentations*

Febrile stroke
Renal failure of unknown cause
Multilobed pneumonia
Septic arthritis
Arrhythmias or heart block
Polyarthritis
Pericarditis
Major artery embolus
Thrombocytopenia

Most clinicians are aware of the usual presentations of endocarditis but it is worthwhile to keep in mind some less common modes of onset, many of which the housestaff here at Harbor General Hospital have been confronted with during the past 18 months (see Table II-2). In patients with cardiac decompensation, the presence of these ancillary syndromes may alert physicians to an underlying endocarditis.[3]

The results of routine laboratory tests available at short notice may not be too useful in the early diagnosis of endocarditis. One that is simple, rapid and very helpful is the microscopic examination of a urine specimen; hematuria is found to be present in most patients with endocarditis when it is looked for repeatedly.[1,6]

The laboratory test of paramount importance, of course, is a blood culture. In an urgent situation, where therapy will often be initiated empirically before the organism can be identified, four or five sets of cultures (aerobic and anaerobic) of blood specimens obtained from different venous sites are optimum.[7,8] These can be taken a short time apart because the bacteremia tends to be more or less constant at a particular level for each individual case.[3] In addition, cultures are most often positive on the first set.[7-9] The purpose of multiple cultures is to identify those patients in whom bacteremia may be fluctuating at a relatively low level.

Findings in recent studies continue to show the viridans and Group D streptococci as the most frequent microbial agents found in patients with endocarditis, followed by the staphylococci, both aureus and albus. These organisms make up 80 to 90 percent of those isolated in nonselected populations.[1-3,9] However, in 173 recently reported patients with heroin-associated endocarditis,[10-16] staphylococci accounted for 94 of these cases, followed by Streptococcus viridans in only 19 cases. There were also 13 patients with aerobic Gram-negative bacillary endocarditis, 11 with Candida, 9 with Group D streptococci and 3 cases caused by microaerophilic streptococci. Consequently, one can see that knowledge of the population being examined will make a difference in the types of organisms that should be expected. In addition to drug abusers using intravenous administration, there are other clinical situations in

TABLE II-3.—*Key Etiologic Associations in Infective Endocarditis*

Clinical Situation	*Organism(s) Often Found*
Alcoholism	Pneumococci
Narcotic abuse	Staphyloccus aureus, Group D streptococci, Gram-negative rods, fungi
Hospital acquired	Penicillin-resistant streptococci and staphylococci and Gram-negative rods
Urologic or gynecologic manipulations	Enterococci
Prosthetic cardiac valves	
Early (<60 days postop)	Penicillin resistant staphylococci (especially albus), Gram-negative rods, fungi (especially Candida)
Late (>60 days postop)	Viridans and Group D streptococci and penicillin-sensitive staphylococci
Endocarditis with major embolus	Fungi, Gram-negative rods, staphylococci

which certain organisms tend to be found (see Table II-3).

In chronic alcoholics there is a propensity for pneumococcal endocarditis to develop,[17,18] while in patients in hospital endocarditis with penicillin-resistant streptococci and staphylococci as well as aerobic Gram-negative rods tend to develop.[19,20] In patients with endocarditis where there have been earlier urologic or gynecologic manipulations, the Enterococcus is often the cause.[21] In cases where the initial presentation is a major arterial embolism, staphylococci, fungi and Gram-negative rods (both aerobic and anaerobic) predominate as etiological agents.[20,22-24] In the presence of a prosthetic cardiac valve, one sees two distinct distributions of organisms causing endocarditis, by separation of the cases to an early (less than 60 days postoperative) versus late (more than 60 days postoperative) form.[25] In the first group, penicillin-resistant staphylococci, especially the coagulase negative variety (Staphylococcus albus); Gram-negative rods, and fungi, especially Candida species, are frequent isolates, while in the latter group, viridans and Group D streptococci and staphylococci (which may be penicillin-sensitive) are usually seen.[25]

Culture negative endocarditis makes up, on an average, 15 percent of proven cases of infective endocarditis.[8,22] The most common cause of this phenomenon is probably previous antibiotic therapy.[8] Another cause is fungal endocarditis where the fungemia tends not to be as constant as in bacterial endocarditis.[26] Coxiella burnetti (Q fever), psittacosis and viruses have been described to cause an acute destructive valvulitis[1,22,27-29] and will also present as culture-negative endocarditis. Since ordinary laboratory techniques will not isolate these agents, the diagnosis is best made by specific serologic tests. Endocarditis caused by anaerobic organisms may be missed unless proper transport and cultural techniques are used.[22,24]

In patients with acute cardiac decompensation in whom endocarditis is suspected, a clinician often has to initiate antibiotic therapy either before the results of blood cultures are known, or before definitive sensitivity testing is done. Therefore, an understanding of what organisms to anticipate in a given patient is very helpful. It is a tenet in the treatment of infective endocarditis that a bactericidal agent or agents be used.[1,2] Also, in urgent situations, therapy designed to achieve the most rapid killing should be sought.

For penicillin-sensitive streptococci, penicillin alone in doses of 15 to 20 million units per day, administered intravenously for four to six weeks is usually adequate.[2] However, when there has been cardiac failure, the addition of an aminoglycoside such as streptomycin may be important because this combination increases the rate of killing.[30]

If a patient has a definitive history of a major penicillin allergy (such as anaphylaxis or giant urticaria), one should substitute one of several regimens that have been efficacious against penicillin-sensitive streptococcal endocarditis. Cephalothin (90 to 150 mg per kg of body weight per day given intravenously), vancomycin (30 mg per kg of body weight per day given intravenously) and the combination of erythromycin (60 mg per kg of body weight per day given intravenously) plus streptomycin (30 mg per kg of body weight per day given intramuscularly) have each been utilized in penicillin allergic patients.[31]

If a patient has a history of a minor allergy to penicillin, such as skin rash, skin tests can be carried out with the major and minor antigenic determinants of penicillin to predict the likelihood of anaphylaxis.[32] In the absence of this facility, one should either use an alternate therapeutic regimen or with the help of an allergist, institute rapid penicillin densensitization.[2]

In recent studies of Group D streptococcal en-

docarditis, nearly half of the isolates from such cases are not true enterococci but are Streptococcus bovis.[33-36] This is extremely important because S. bovis is usually sensitive to penicillin as well as to a whole host of other single antibiotics. The mortality in endocarditis due to this organism is fairly low, whereas true enterococci (S. faecalis) are difficult to eradicate with single antibiotics, require combination chemotherapy and result in mortality three times that of S. bovis endocarditis.[33-36] For S. bovis, penicillin in doses of 15 to 20 million units per day given intravenously is the treatment of choice. There is some evidence that the addition of an aminoglycoside will enhance the rate of killing.[34,37] For Streptococcus faecalis, the regimens of choice are combinations of penicillin or ampicillin (150 to 250 mg per kg of body weight per day given intravenously) plus an aminoglycoside.[2,21,38,39-41] For patients allergic to penicillin, vancomycin plus an aminoglycoside should be used.[40,42]

When staphylococcal endocarditis is suspected or diagnosed, therapy with penicillinase-resistant antibiotics should be initiated. Methicillin (100 to 200 mg per kg of body weight per day given intravenously), nafcillin (50 to 90 mg per kg of body weight per day given intravenously) or cephalothin (90 to 150 mg per kg of body weight per day) can be used.[1,2] In patients allergic to penicillin, vancomycin should be given.[1,2,31,43,44]

For a patient who presents with cardiac decompensation and presumed bacterial endocarditis and is not an abuser of drugs taken intravenously, expectant therapy with penicillin and streptomycin is usually adequate.[1] This also applies to such similar cases as those of patients in whom blood cultures remain negative. For drug users, staphylococci, Group D and non-Group D streptococci, and aerobic Gram-negative rods must be anticipated and appropriate antimicrobial therapy for all these potential pathogens should be initiated, at least until positive blood cultures have returned. An initial regimen such as penicillin-methicillin-gentamicin should

TABLE II-4.—*Overall Mortality in Treated Cases of Infective Endocarditis in the Recent Literature**

Organism	*Cases*	*Deaths*	*Percent Died*
Streptococcus viridans[9,14,16,19,25,30,36]	134	24	18
Streptococcus bovis†[33-36]	37	5	14
Streptococcus faecalis†[33,35,36]	26	9	32
Penicillin-sensitive anaerobes[24,45]	36	8	22
Prosthetic valve endocarditis (excluding fungal)[25]	45	18	40
Gram-negative rods			
Aerobic[23,46]	30	17	57
Anaerobic (penicillin resistant)‡[24,25]	27	11	41
Staphylococcus aureus[1,14,16,20,25]	87	29	33
Fungal (mainly Candida)[26,48]	155	140	90

*Includes both appropriate antimicrobial as well as surgical therapy where indicated.
†From recent series in which S. bovis is adequately differentiated from S. faecalis.
‡Bacteroides fragilis mainly.

TABLE II-5.—*Adverse Factors in Survival of Patients with Infective Endocarditis*

	Example
Virulent organism	Staphylococci, GNR, pneumococci
Old age	
Serious systemic disease(s)	Diabetes mellitus, narcotic addiction, alcoholism, cancer
Serious underlying cardiac disease	Hypertension, coronary artery disease, rheumatic heart disease
Aortic or mitral valve involvement	
Prosthetic valve involvement	
Propensity of organism to embolize	Fungi, anaerobes, staphylococci
Presence of paravalvular infection	Ring abscess, myocardial abscess
Difficulty killing organism	Streptococcus faecalis, penicillin-resistant, GNR anaerobes, fungi, Q-fever
Toxicity of therapy	Aminoglycosides, amphotericin B
Cardiac surgery often necessary	Anaerobic and aerobic GNR, fungi, Q-fever
Presence of congestive failure	

GNR = Gram-negative rods

be effective. In patients allergic to penicillin, a combination of vancomycin and gentamicin could be substituted with similar salutory effects.

In anaerobic bacterial endocarditis in which the organisms are sensitive to penicillin, cures have been achieved with this drug.[24,45] However, if the organism is resistant to penicillin, such as Bacteroides fragilis, or if a patient is truly allergic to penicillin, bacteriostatic agents such as clindamycin or chloramphenicol would have to be used. The success with these agents has been variable.[24,45]

For aerobic Gram-negative bacillary endocarditis, drugs such as gentamicin, kanamycin, chloramphenicol, ampicillin, tobramycin and carbenicillin have been used alone or in various combinations according to sensitivity data.[23,46] Amphotericin B remains the only useful agent for fungal endocarditis.[1,16,47]

The response to medical therapy of the last three forms of infective endocarditis has been disappointing, and surgical intervention frequently is required.

Although in patients with endocarditis due to penicillin-sensitive organisms there is a recovery rate of 75 to 95 percent, for those in whom other types of organisms are present there is much higher mortality (see Table II-4). This ranges from 30 to 40 percent mortality for Staphylococcus aureus, true enterococcal, penicillin-resistant anaerobic Gram-negative rod and prosthetic valve endocarditis (of all bacterial causes) to about 90 percent mortality for fungal endocarditis reported from previous series. However, a recent report of 11 patients with Candida endocarditis yielded much higher survival rates than have previously been cited.[26,47,48] In this study, early diagnosis and surgical intervention (within 48 hours of confirmation of the diagnosis) plus vigorous intraoperative and prolonged, postoperative therapy with amphotericin B, resulted in eight cures. The somewhat lower mortality rates in recent series of staphylococcal endocarditis[1,14,16,20] reflect the increasing proportion of heroin addicts with this disease and the frequent occurrence of tricuspid involvement in such patients. The addict population tends to have reasonably good nutritional status without significant medical problems before endocarditis develops,[14] and infection of the tricuspid valve carries a better prognosis than endocarditis of either aortic or mitral valves[14] because of the more benign hemodynamic consequences and lack of direct access of septic emboli to more vital organs.

In addition to the virulence of the organism involved,[1,14] other factors tend to increase mortality in cases of infective endocarditis (see Table II-5). In older patients, for a variety of reasons, there is a higher death rate.[1,14] Patients with serious underlying cardiac or systemic diseases do not fare as well as those without these conditions. In those with aortic or mitral involvement and those in whom congestive heart failure develops there is a worse prognosis.[1,14,49] If there is a paravalvular infection, such as a valve-ring abscess or a myocardial abscess, or if there has been peripheral embolization causing vital organ damage or metastatic abscesses, the survival rate is significantly diminished.[1,14,20,50] Also, if the offending organism is difficult to eradicate with presently available therapy or the therapy intrinsically has significant toxicity, as with the aminoglycosides and amphotericin B, the mortality is exceedingly high.[1,21,23,24,45,51,52]

The principal causes of death in patients with infective endocarditis varies somewhat, depending on which valves of the heart are involved. In those with principally left-sided involvement, cardiovascular causes, mainly congestive heart failure, predominate, with neurologic complications due to central nervous system embolization of lesser importance.[50] In contrast, those with right-sided infective endocarditis die usually from both generalized as well as localized infections (principally pneumonia and meningitis) and less often from congestive heart failure.[18]

The Hemodynamic Basis for Atypical Physical Findings in Acute Valvular Regurgitation

J. Michael Criley, MD* and Arnold H. Blaufuss, MD:† Infective endocarditis poses two major challenges: to isolate and treat the organism quickly and effectively, and to localize and assess the hemodynamic significance of the cardiovascular lesion or lesions. Dr. Bayer has dealt with the bacteriological aspects, and these remarks will concern themselves with valvular lesions.

Unlike rheumatic heart disease, infective endocarditis may create severe valvular incompetence in a short time, and as a result the impact on the patient may be quite different and the resulting clinical findings may be quite confusing. The fol-

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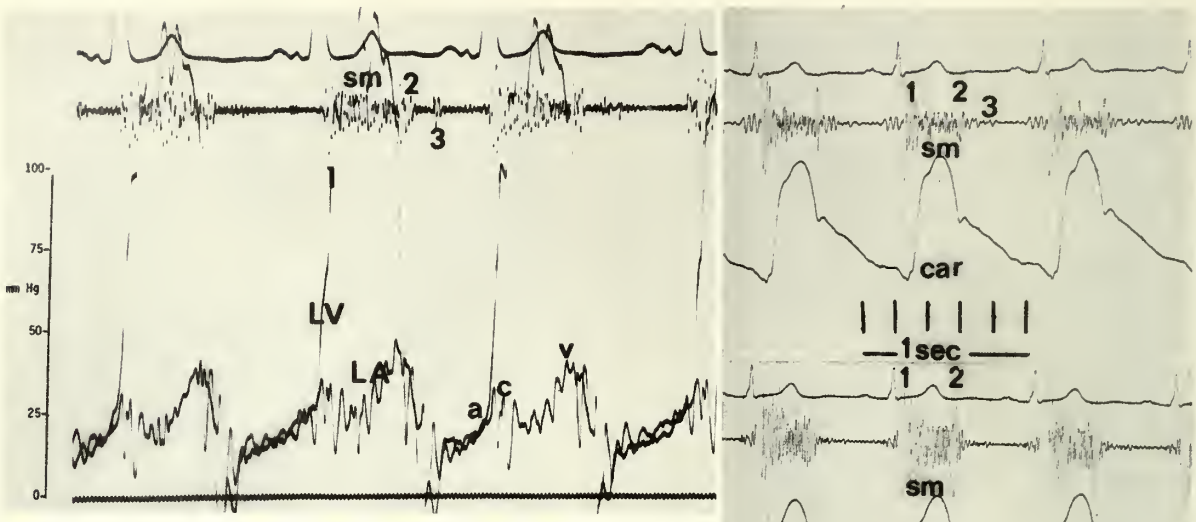


Figure II-1.—Chronic Mitral Regurgitation—**Left,** left atrial (LA) and left ventricular (LV) pressure in a 21-year-old minimally symptomatic man with a history of recurrent acute rheumatic fever. The left atrial "V" waves (V) are prominent, and followed sequentially by a rapid "y" descent and rapid filling wave as the large volume within the atrium is rapidly expelled into the ventricle. The phonocardiogram shows an intact first sound (I), a holosystolic murmur (sm) and a prominent third heart sound (3). The third sound results from the rapid early diastolic inflow into the ventricle. There is no S-4, and the atrial contraction wave (a) is not prominent. Time lines =.04 sec. **Right,** a low frequency phonocardiogram (upper panel) shows the third heart sound (3), while a medium frequency recording (lower panel), better shows the systolic murmur (sm) which occupies all of systole and on some cycles continues after the second sound (2). CAR=carotid pulse tracing.

lowing is a summary of our findings in a group of 16 patients with infective endocarditis studied by cardiac catheterization, phonocardiography and echocardiography at Harbor General Hospital in the past three years.

Tricuspid regurgitation, in its usual setting in rheumatic heart disease (RHD), produces a left parasternal systolic murmur with inspiratory augmentation, large V waves and a pulsatile liver. Many of these findings in patients with RHD are due to the presence of pulmonary hypertension, resulting from concurrent mitral valvular disease. In acute infective endocarditis, there may be only a soft early systolic murmur (or no murmur at all) and a normal venous pressure unless septic pulmonary emboli produce significant pulmonary vascular obstruction to cause right ventricular pressure overload.

Mitral regurgitation in RHD (see Figure II-1) is associated with a holosystolic apical murmur, an early diastolic gallop sound (S-3) and a volume overload to the left atrium and ventricle resulting in gradual enlargement of these two chambers over a period of time. Significant pulmonary hypertension is unusual, since the large left atrium can accept the regurgitant volume quite well. However, acute mitral regurgitation (see Figure II-2) has a devastating impact on the relatively noncompliant left atrium, raising its pressure to 75 to 100 mm of mercury in systole. To make matters worse, the left ventricle is also limited in its ability to accept a volume load, and the response is an increase in diastolic pressure. Therefore the left atrium is subjected to double jeopardy, a high systolic volume and pressure which it cannot get rid of in diastole. The result is a mitral stenosis-like pulmonary hypertension, pulmonary congestion and pulmonary arterial hypertension. The murmur may be mistaken for an ejection murmur, and accompanied by a presystolic gallop sound (S-4). The reason for the unusual quality of the murmur is that the noncompliant left atrium "refuses" any more regurgitant blood in late systole because its pressure rivals the end systolic left ventricular pressure. The S-4 results from the relatively large atrial systolic contribution to the filling of the noncompliant left ventricle.

Aortic regurgitation may present very atypical clinical features when the lesion occurs acutely. A clinician who expects the bounding "water hammer" pulse, enlarged hyperactive left ven-

tricle, long decrescendo diastolic murmur and two-phase Austin Flint rumble (see Figure II-3) may be surprised by the unusual features of acute, sudden onset aortic regurgitation.

In infective endocarditis, aortic valvular destruction may occur almost instantaneously, and the left ventricle cannot adjust to the increased diastolic volume load. The noncompliant ventricle consequently exhibits a notably elevated diastolic pressure which may exceed left atrial pressure shortly after the mitral valve opens, resulting in preclosure of the mitral valve (see Figure II-4). This preclosure leads to obliteration of the first heart sound, and frequently causes a loud mid-diastolic murmur as the valve closes while a large volume of blood is leaving the left atrium. The Austin Flint murmur always implies significant aortic regurgitation, but when confined to mid-diastole and associated with an attenuated or absent first heart sound, it is indicative of very severe disease. The rapid elevation of left ventricular diastolic pressure may abbreviate the aortic regurgitant murmur as well as artificially support the aortic diastolic pressure, and consequently attenuate two valuable signs of aortic regurgitation.

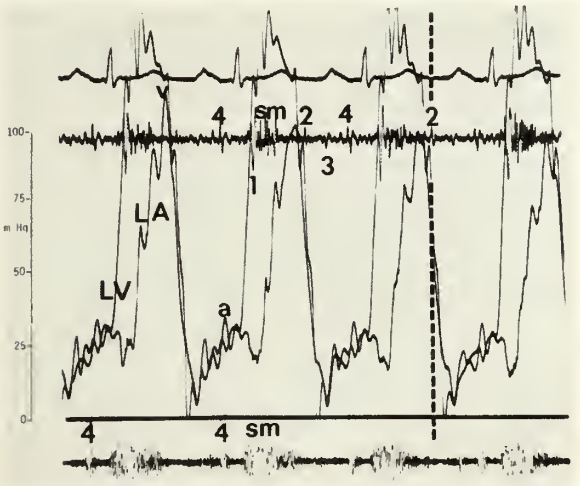


Figure II-2.—Acute Mitral Regurgitation—In contrast to the patient illustrated in Figure II-1, this 48-year-old man is severely symptomatic with pronounced dyspnea and orthopnea of sudden onset during a febrile illness. Findings on an x-ray film of the chest were interpreted as bilateral pneumonia, and the heart murmur was initially thought to be due to aortic stenosis because of its medium length crescendo-decrescendo character and associated fourth heart sound. Six blood cultures were positive for group D alpha streptococcus, and he was successfully treated with penicillin and streptomycin. His hemodynamic status only permitted bed-to-chair activity, and cardiac catheterization was carried out for evaluation of probable ruptured chordae tendineae. He was found to have pronounced pulmonary hypertension, striking "V" waves in the left atrium of over 100 mm of mercury and pronounced elevated left ventricular end diastolic pressure (33 mm of mercury) with prominent "a" waves. The apical systolic murmur (sm) ended well before the second sound (2, dashed line) because the left atrial pressure was sufficiently high to impede late systolic regurgitation. The fourth sound (4) resulted from a vigorous atrial contraction (a). A soft third sound (3) was recorded, but not easily heard. Time lines=.04 sec.

Angiography showed a flail anterior mitral leaflet. Valve replacement was carried out, and the patient is currently asymptomatic.

Echocardiography

Echocardiography may be extremely helpful in identifying those patients described above with endocarditis and acute mitral insufficiency. Instead of a thickened and often restricted anterior mitral leaflet as usually seen in rheumatic mitral insufficiency (see Figure II-5), the anterior mitral leaflet in endocarditic mitral regurgitation will be thin and delicate with increased excursion (see Figure II-6). When rupture of chordae tendineae occurs, the anterior leaflet excursion may be notably exaggerated. In addition, vibrating echoes continuous with the anterior mitral leaflet may identify mitral valve vegetations. It should be noted that similar findings are seen on the tricuspid valve and should be looked for in patients in whom right-sided infective endocarditis is suspected.

Similarly, echocardiography can be extremely helpful in assessing the impact of aortic regurgitation (see Figures II-7, II-8, II-9). The presence of the triad of fluttering of the anterior mitral valve preclosure, and large excursions of the left ventricular walls, is diagnostic of severe valvular incompetence and indicative of a poor outcome without surgical intervention. Occasionally, vibrating echoes in the aortic root at the level of the aortic valve may identify vegetations on the cusps. In addition vibrating echoes in the left ventricular outflow tract may suggest the presence of aortic cusp vegetations with prolapse into the left ventricular outflow tract (see Figure II-8).

The ventricular dimensions and hyperkinesis of the septum and posterior left ventricular wall are indistinguishable in acute severe mitral and aortic insufficiency, as both present a sudden volume overload to the left ventricle. Particularly noteworthy in the presence of severe valvular incompetence is early diastolic diastasis or flattening of the left side of the interventricular septum and left ventricular posterior wall (see Figure II-9) as the ventricle reaches maximum compliance

in early diastole because of the large volume overload. Small posterior pericardial effusions may also be seen (see Figure II-9), but large effusions are distinctly rare in infective endocarditis.

Summary and Conclusions

The confusing physical findings presented by patients with infective endocarditis should not mislead a physician into assuming that there is extensive myocardial damage and not severe valvular regurgitation because of the paucity of murmurs, loud gallop sounds and soft or absent first sound. Echocardiograms have been invaluable in assessing valve function and provide an accurate noninvasive method for serially studying the size and performance of the left ventricle.

It is hoped that this treatise on the hemodynamic basis for atypical findings will stimulate a more aggressive use of noninvasive instruments, including the stethoscope, in the management of these desperately ill patients.

Dr. Oill: Before Dr. Bayer discusses infectious pericarditis and myocarditis, I will briefly review the clinical signs and symptoms associated with these diseases.

In patients with infectious pericarditis there may be evidence of acute pericarditis alone or significant pericardial effusion and tamponade may be noted in addition. In acute pericarditis, precordial pain is common—sometimes mimicking a myocardial infarction—and is frequently affected by respiratory movements, cough and position. Because of inflammation of the adjoining diaphragmatic pleura it is not uncommon for the pain to be referred to the left supraclavicular area. It may have the distinction of being intensified by swallowing due to involvement of the esophagus. Rarely the pain is throbbing and synchronous with the heart beat.

The primary feature noted on physical examination of patients with acute pericarditis is the presence of a pericardial friction rub. Typically the rub is triphasic, consisting of a presystolic component corresponding to atrial systole, a systolic component and an early diastolic component. Fever is common, as is tachycardia.

If the pericarditis is associated with a significant effusion, the friction rub may be obliterated with the presence, then, of an increased area of cardiac dullness, muffled heart sounds, cyanosis (occasionally) and a paradoxical pulse. The presence of pulsus paradoxus indicates a significant pericardial effusion.

Physical findings in a patient with pericardial tamponade are dependent on the hemodynamic deficits present. Neck vein distention is prominent with a rapid x descent in the jugular venous pulse. The y descent is not prominent as is seen in constrictive pericarditis.[53] Tachycardia is usually present to maintain cardiac output and as the stage of tamponade is approached there is a drop in pulse pressure. A complete discussion of the clinical, electrocardiographic, radiologic and pathophysiologic manifestations of pericarditis, pericardial effusion and tamponade can be found in a symposium previously published in this journal.[54]

The typical clinical features of myocarditis are

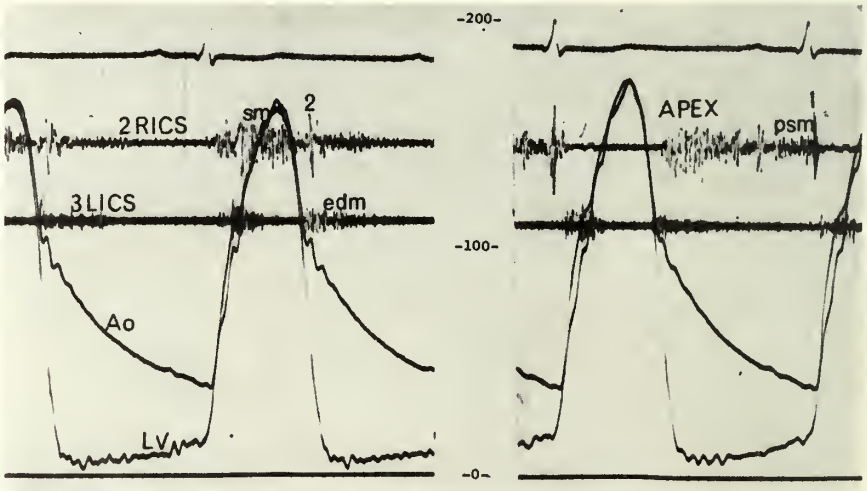


Figure II-3. — Chronic Aortic Regurgitation — A 30-year-old woman with childhood rheumatic fever was minimally symptomatic, but was noted to have progressive cardiac enlargement on serial x-ray studies of the chest. The bounding arterial pulses are shown in the aortic (Ao) pressure of 175/40. The left ventricular end diastolic pressure is minimally elevated (18 mm of mercury). A loud ejection systolic murmur (sm) due to high flow was heard in the aortic area (**left panel**, sm), and a high-pitched early diastolic murmur of aortic regurgitation (edm) was heard at both sides of the sternum. At the apex (**right panel**) a two component Austin Flint murmur was heard, indicated forward flow across a functionally restricted mitral orifice throughout all of diastole.

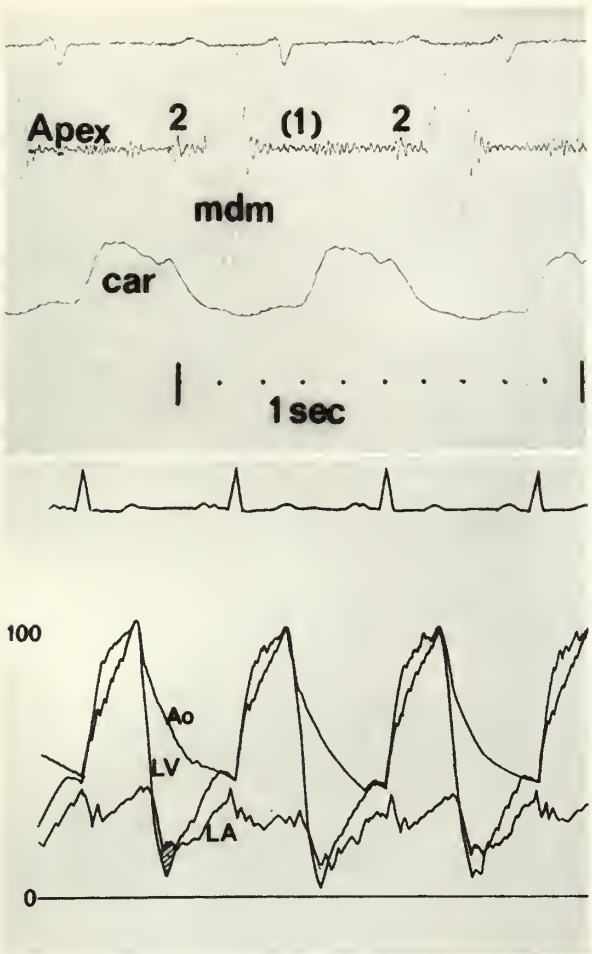


Figure II-4.—Acute Aortic Regurgitation—This 43-year-old heroin addict presented with a febrile illness complicated by a cerebral vascular accident. Multiple blood cultures grew Lactobacillus and Streptococcus viridans. **Above,** on physical examination there were a normal pulse contour and a loud peculiar diamond-shaped murmur (mdm) which could be timed by its relationship to the carotid artery pulse (car), and was found to be confined to middiastole. Many auscultators misinterpreted the murmur as an ejection systolic murmur because of its intensity and configuration. **Below,** cardiac catheterization showed a notably elevated left ventricular (LV) diastolic pressure which rose steadily from the early diastolic nadir until it reached aortic (Ao) pressure in middiastole. The left atrial (LA) pressure was exceeded in early diastole, and the mitral valve closed and remained closed throughout two thirds of diastole (see Figure II-8). The only period available for mitral inflow was during the time when left atrial pressure equaled or exceeded left ventricular pressure (shaded area). The timing of the middiastolic murmur suggests that closure of the mitral valve in the face of a high rate of atrioventricular flow increased the velocity of the blood flowing through the closing orifice resulting in pronounced turbulence.

After the patient's condition stabilized following the cerebral vascular accident, successful aortic valve replacement was carried out. The aortic valve was found to be in shreds, with a large prolapsing vegetation extending down into the left ventricle.

fatigue, dyspnea, palpitations and occasionally precardial pain. This is followed during the first few weeks of a systemic infection by cardiac enlargement, a cardiac murmur or pericardial friction rub, a faint first heart sound, gallop rhythm and pulsus alternans.[55] There is a persistent fever, with tachycardia disproportionate to the degree of fever. Arrhythmias are common. This symptom complex is associated with a variable degree of rhythm disturbances, conduction defects and ST-T wave electrocardiographic abnormalities.[56]

Now Dr. Bayer will review the subject of infectious pericarditis and briefly mention the various causes of myocarditis.

Infectious Pericarditis

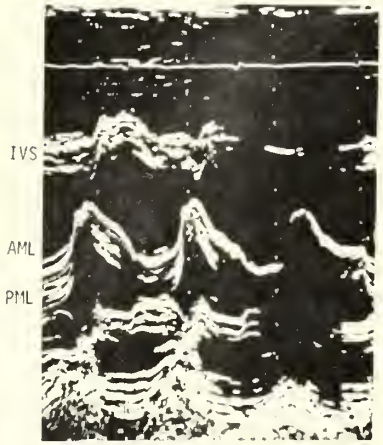
Dr. Bayer: The more common forms of infectious pericarditis are listed in Table II-6. It is, of course, difficult at times to differentiate between infectious and noninfectious pericarditis, as well as between the various etiologic agents in pericarditis due to an infection. The signs and symptoms are often identical. However, there are certain infectious agents that may cause a rapid inflammatory or effusive pericarditis with hemodynamic decompensation in which early diagnosis and specific antimicrobial therapy or surgical therapy (or both) are mandatory and often life-saving.

Of all the infectious causes, purulent bacterial pericarditis is the one that most often presents with gross cardiac dysfunction. What are some of the clinical clues that might assist us in anticipating this disease entity? Understanding the pathogenesis of purulent pericarditis is extremely helpful. The four basic mechanisms for this process are (1) contiguous spread, (2) hematogenous spread from a distant source, (3) hematogenous spread from a local source and (4) external, direct inoculation. The most common clinical situation in which contiguous spread occurs is in patients with pneumonia or empyema. Osteomyelitis and soft tissue infections are common precursors for the distant hematogenous spread. Local hematogenous spread may occur in patients with infective endocarditis from coronary embolization to the myocardium, and then rupture of such abscesses into the pericardial sac.[57-59] Penetrating wounds to the pericardium or bacterial implants during open heart surgical procedures are other causes of bacterial pericarditis.[59]

The most common etiologic agents in this disorder are staphylococci, pneumococci and

streptococci.[60] There were a moderate number of meningococci noted in the large series by Pearce, Guze and Boyle,[60] and this agent continues to be associated with pericarditis in more recent reports.[61-63] In children, Hemophilus influenzae is a common offender.[64]

It is important to look for the underlying clinical situation in which purulent pericarditis develops, as it often enables clinicians to anticipate certain organisms. If an adjacent pleuropulmonary infection is present, pneumococci will often be the pathogen involved.[65] Staphylococcal osteomyelitis and localized abscesses like furuncles often provide sources for hematogenous spread to the heart. A myocarditis with subsequent abscess formation probably occurs, from which bacteria enter the pericardium.[65-67] The diagnosis of meningococcal pericarditis is often associated with a coincident meningitis or meningococcemia or both.[63,68,69] Two separate mechanisms seem to



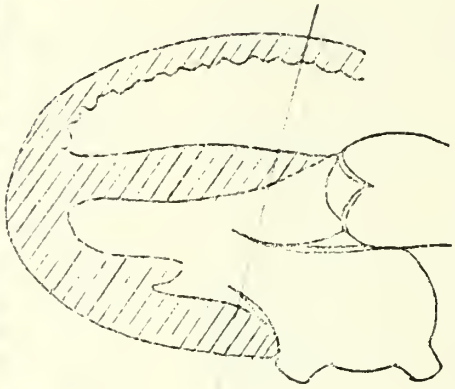
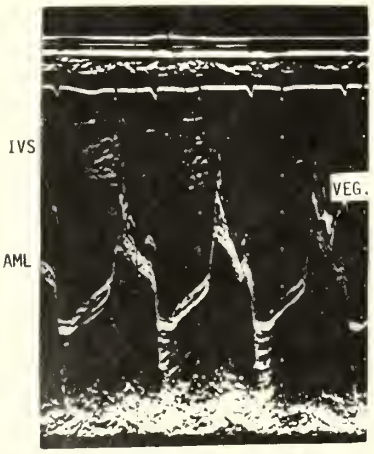


Figure II-5.—A 56-year-old man with chronic rheumatic mitral regurgitation. Note the thickened anterior (AML) and posterior (PML) mitral leaflets with normal posterior motion of posterior mitral leaflet. Atrial fibrillation is present. IVS = Interventricular septum.



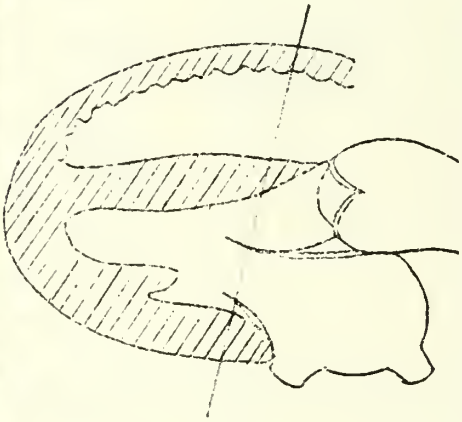
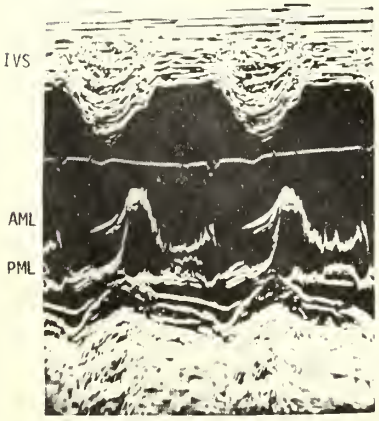


Figure II-6. — A 26-year-old woman with acute infective endocarditis (Streptococcus faecalis) and severe, acute aortic and mitral insufficiency. Echocardiogram reveals increase excursion of a thin anterior mitral leaflet (AML) with shaggy echoes at the tip suggesting an anterior leaflet vegetation. At surgical operation done the same day, the presence of ruptured chordae tendineae with a large friable anterior leaflet vegetation was noted. Severe aortic cusp destruction was also present and double valve replacement was carried out.



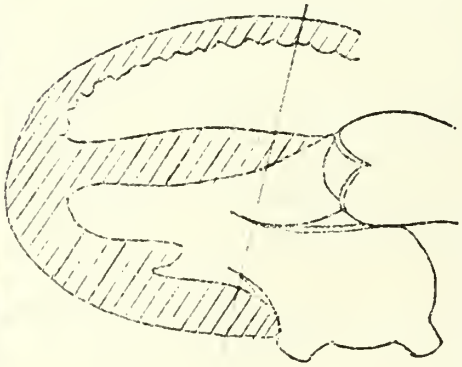


Figure II-7.—A 21-year-old man with chronic aortic insufficiency secondary to rheumatic valvulitis. Pronounced fluttering of the anterior mitral leaflet is seen, no mitral preclosure is present.

be involved in cases of meningococcal pericarditis. One type is seen early in meningococcal infections, and probably is the result of bacteremic seeding of the pericardium. The other is seen later, a week or so after antimicrobial therapy has begun. The latter form is associated with inflammation of other serosal and membrane surfaces, in addition to the pericardium. Therefore, pleural effusions, arthralgias and arthritis are not uncommon.[70-72] All effusions are sterile. The pathogenesis is not certain; however, an immunologic one is suggested. One must be aware of this syndrome because it will respond to anti-inflammatory drugs such as salicylates or corticosteroids, or both, and it is not a sign of failure of the clinician's antimicrobial regimen.[72,73]

The most common and feared complication of purulent pericarditis is cardiac tamponade, and it is the most frequent cause of death.[60] Congestive heart failure from an associated myocarditis may also occur.

If a patient presents with a pericardial effusion and rapidly declining cardiac function, and a clinical background appropriate for purulent pericarditis is present, early diagnosis and management is imperative. The presence of the effusion can be shown most rapidly, and at bedside, using echocardiography.[74] Pericardiocentesis should be immediately carried out by an experienced cardiologist or surgeon both for diagnostic and therapeutic purposes. The characteristics of the pericardial fluid obtained are very helpful. It is usually frankly purulent with high levels of protein and a cell count with predominantly polymorphonuclear leukocytes. The glucose value may be low in comparison with peripheral levels. The key information is given by findings on Gram stain; the etiologic agent can often be identified and knowledge obtained to guide the physician in determining the appropriate choice of initial antibiotic coverage. The pericardial fluid should also have an acid-fast bacillus (AFB) stain made on it and it should be submitted for appropriate bacteriologic, fungal, viral and mycobacterial cultures.

In adults, where initial findings on Gram stain may not be helpful, antibiotic regimens to cover pneumococci, staphylococci, streptococci and meningococci should be instituted until final bacteriologic identification is obtained. Penicillin in

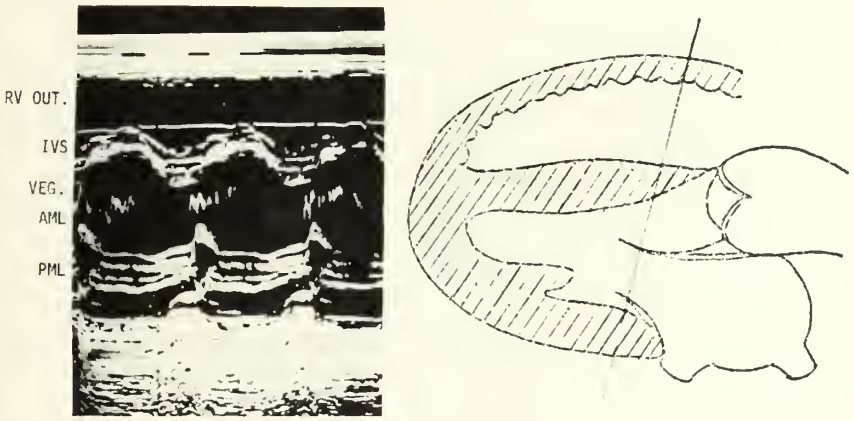


Figure II-8.—A 43-year-old heroin addict with lactobacillus endocarditis, severe acute aortic insufficiency, and an embolic cerebral vascular accident. Note the mitral valve preclosure with a shaggy vegetation (VEG) in the left ventricular outflow tract. Also present is hyperkinetic septal motion (IVS) and a dilated left ventricle.

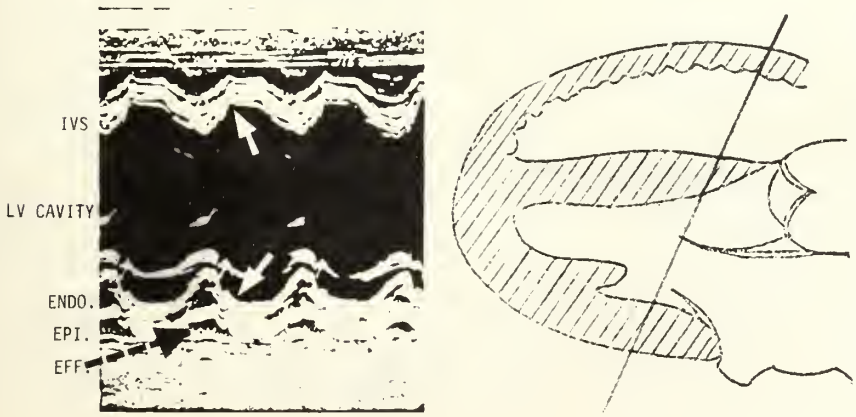


Figure II-9. — A 20-year-old woman with candida endocarditis, acute severe aortic regurgitation and embolic occlusions of both femoral arteries. Shown is a dilated left ventricle with pronounced hyperkinesis of the interventricular septum (IVS) and left ventricular posterior wall with early diastolic diastasis (arrows) indicating maximum ventricular compliance occurs early in diastole. Also present is small posterior pericardial effusion (EFF). ENDO = endocardium; EPI = epicardium.

TABLE II-6.—*Causes of Infectious Pericarditis*

Viral
Coxsackie, ECHO
Influenza
Infectious mononucleosis (EBV, CMV)
HBV
Bacterial
Granulomatous
Tuberculous
Fungal (coccidioidomycosis, histoplasmosis)
Spirochetal
Syphilitic
Spirillum
Leptospiral
Mycoplasmal
Parasitic
Toxoplasmal
Amebic
Echinococcal
Trichinosis

EBV = Epstein-Barr virus
CMV = Cytomegalovirus
HBV = Hepatitis B virus

doses of 15 to 20 million units per day given intravenously plus methicillin, 8 to 12 grams per day given intravenously, would be one such combination. In a penicillin-allergic patient, therapy with chloramphenicol in doses of 4 to 6 grams per day given intravenously and vancomycin, 2 grams per day given intravenously, could be instituted. In the pediatric population, ampicillin in doses of 150 to 250 mg per kg of body weight per day given intravenously, should probably be substituted for penicillin to cover Hemophilus influenzae. If pericardial fluid reaccumulates, this can be controlled by a variety of surgical drainage techniques.[59,60,67,75] With early recognition of this disease, prompt and appropriate antimicrobial therapy, and adequate surgical drainage, survival rates of 50 to 75 percent can be reached.[59,60]

Tuberculous pericarditis is usually a chronically progressive infection but on occasion can present at an early stage with cardiac decompensation.[60] Tuberculous pericarditis may be due to extension of a caseous focus in the mediastinum to the pericardium or as part of hematogenous seeding, so that on an x-ray film of the chest there may be an apparently normal pulmonary parenchyma. What other clues can a clinician seek to help diagnose a tuberculous cause in an emergency situation? Skin testing with tuberculin is helpful, giving positive findings in most cases of tuberculous pericarditis.[76] However, the necessary delay before skin test results are available (48 to 72 hours) limits the test's usefulness in urgent cases.

There are two pieces of data that can be obtained quickly and may prove very helpful. One results from examination of pericardial fluid.[77] In tuberculous pericarditis, the fluid is serous or serosanguinous, and is not frankly purulent. The protein content is high (exudate), as is the cell count. In acute infection, there may be predominantly polymorphonuclear cells. AFB smears of the fluid are occasionally positive. Culture of pericardial fluid will be positive in between 25 and 50 percent of patients, with the yield somewhat higher if a pericardial biopsy specimen is taken. However, in an emergency situation, one cannot afford the wait of several weeks for return of culture results. The second important clue to search for is evidence of extracardiac tuberculous involvement.[78] A positive acid-fast smear from sputum, gastric aspirates, pleural fluid, cutaneous lesions, and so forth, will aid in diagnosing a tuberculous cause. If tuberculous pericarditis is suspected, even if the evidence is scanty, antituberculous therapy with two effective agents such as isoniazid and ethambutol should be instituted immediately. Administration of corticosteroids may be useful in the short term, under antituberculous coverage, for control of the pericardial effusion.[79]

Although histoplasmosis is the most common cause of fungal pericarditis nationally, in the western section of the country, coccidioidal infections are more prevalent. What are some clues to the early diagnosis of coccidioidal pericarditis in the acute situation when hemodynamic deterioration is present? Of course, recent travel history, residence or work in an endemic area is helpful information. Prominent hilar or paratracheal node enlargement may be seen on an x-ray film of the chest.[80] The leukocyte differential may show a high level of eosinophilia.[81] Findings on skin testing with coccidioidin may not be too helpful as they are most often negative in the face of widespread dissemination.[82] Conversely, positive results on a test without knowledge of prior reactivity gives one little information concerning the time of antigenic exposure. Specific serologic tests are very helpful in diagnosing an early, acute coccidioidal infection but are usually not available on very short notice.[83]

Like tuberculous pericarditis, the presence of typical coccidioidal spherules in pericardial fluid or in extracardiac sites—especially sputum, pleural fluid or skin lesions—makes it nearly certain that this agent is responsible for the pericarditis. Amphotericin B remains the only useful agent for coccidioidal infections.

Amebic pericarditis is a well-known, though fortunately uncommon, sequela of hepatic amebic abscess. The abscess is almost invariably located in the left lobe of the liver with extension through the diaphragm into the pericardial sac.[84] This is an aggressive pericarditis with rapid tamponade often ensuing. A history of travel by the patient into an endemic area is useful information, but the most helpful diagnostic history obtained is of an abdominal, subdiaphragmatic process. A history of retrosternal pain, nausea, vomiting, cough, dyspnea, fever, shoulder pain and right upper quadrant tenderness sometime prior to the onset of frank cardiovascular symptomatology can usually be elicited.[85,86]

The diagnosis depends first on detecting the presence of a liver abscess by hepatic scan and abdominal echogram. Serologic tests (complement fixation or indirect hemagglutination) for Entamoeba histolytica are usually positive in high titer with hepatic amebiasis in more than 90 percent of patients[84] and are supportive evidence for this diagnosis, once an abscess has been shown present; negative serologic tests make the diagnosis doubtful. These tests can now be carried out and results made available at some institutions with relative speed. Examinations of either abscess fluid, pericardial fluid or stool are not usually rewarding in looking for the organism.

Because of the virulent nature of amebic pericarditis, once the diagnosis is presumptively made, specific amebicidal therapy should be initiated immediately. Metronidazole (Flagyl®) has been efficacious in treating hepatic amebiasis, but its failure to attain high levels in the myocardium makes its use less attractive in amebic pericarditis.[87] The current regimen of choice is a combination of chloroquine phosphate (250 mg four times a day for 2 days, then twice a day for 28 days) and emetine hydrochloride (1 mg per kg of body weight up to 65 mg maximum per day given intramuscularly) for ten days.

Myocarditis

Table II-7 depicts a partial list of some of the infectious agents that have been associated with myocarditis. The viruses, especially Coxsackie B, are probably the most common etiologic agents. Any of the many organisms listed can cause a myocarditis that is either clinically transient or fulminant and life-endangering. One that deserves special mention is toxoplasmosis. Reports of its causing significant cardiac infection, especially in the setting of the leukemia-lymphoma group of diseases, are on the rise in recent literature and this entity should always be thought of in immunosuppressed patients in whom cardiac failure develops.[88-91]

DR. OILL: Dr. Larry Fisher will now discuss two clinical entities not uncommonly encountered: septic shock or febrile hypotension and disseminated intravascular coagulation.

Septic Shock

LARRY FISHER, MD:* As a cause of clinical shock, sepsis is surpassed in frequency only by hemorrhage and acute myocardial infarction. The most common offending organisms are Gram-negative bacteria, although septic shock may occasionally occur with infections due to Gram-positive bacteria, viruses, rickettsiae and fungi. Infections with Gram-negative organisms are increasing in frequency and at present constitute the most commonly encountered life-threatening infection in patients in general hospitals.

Since recognition of the clinical syndrome of septic shock, many large centers have reported mortality of 11 to 82 percent, with an average of

*Fellow, Division of Infectious Diseases, Harbor General Hospital.

TABLE II-7.—*Established Causes of Infectious Myocarditis*

- Viral
  - Coxsackie (A & B)
  - Adenovirus
  - ECHO
  - Influenza—during recovery phase
  - Rubella
  - Rubeola
  - Mumps—transitory; usually electrocardiographic changes only
  - Infectious mononucleosis
- Bacterial
  - Secondary to purulent pericarditis
  - Secondary to infective endocarditis
- Protozoal
  - Toxoplasmal—in newborns or immunosuppressed patients
  - Trypanosomal (T. cruzii)—acute self-limited and chonic progressive forms
- Toxin-related
  - Postdiphtheritic
- Fungal
  - Histoplasmosis
  - Coccidioidomycosis
- Hypersensitivity
  - Acute rheumatic fever
  - Postmeningococcal—during antibiotic therapy
- Leptospiral
- Mycoplasmal

50 percent.[92] The figure has not changed despite advances in antibiotic and fluid therapy.

The incidence of Gram-negative bacteremia may be as high as 1 percent. If one considers the annual acute hospital admissions in the United States to be 33 million, then over 300,000 episodes of Gram-negative bacteremia may be anticipated yearly.

The clinical setting for Gram-negative bacteremia can be divided into two major groups. In one group there is a known focus or source. Examples include intravenous lines (especially if left in place longer than 72 hours), recent genitourinary manipulation, recent surgical operation (especially abdominal), burns and tracheostomies. An important factor common to all is recent manipulation or breakage (or both) of the host's mechanical defense barriers.

The enteric Gram-negative rods, such as E. coli, Klebsiella, Proteus and Pseudomonas are relatively avirulent in comparison with pathologic organisms such as pneumococcus, staphylococcus and Group A streptococcus, and possess only limited capacity to produce invasive infections in normal hosts. However, many currently used diagnostic and therapeutic procedures provide a route for the access of Gram-negative organisms into the vascular system, or set up local sites for infections.

Results in a number of studies have shown that in-dwelling Foley catheters left to open drainage for three days or longer are associated with an 80 to 100 percent risk of urinary tract infection developing. Findings in other studies indicate that in perhaps as many as 10 percent of these patients with catheter-associated urinary tract infections bacteremia develops. Similarly, other sites of origin, such as the female reproductive tract and the respiratory tract, especially with manipulation, are important sources of bacteremia.

The second major factor for predisposition to Gram-negative bacteremia includes patients with impaired host defenses. The nature and severity of a patient's underlying disease not only influence susceptibility to Gram-negative infections, but also are the major determinants of survival from septicemia.[93] In patients with agranulocytosis, aplastic anemia, leukemia, cirrhosis or diabetes mellitus, and those receiving cancer chemotherapy or immunosuppressive drugs, there is increased incidence of Gram-negative bacteremia. In fact, the severity of the underlying disease is a more important determinant of survival than the species of organism isolated from the blood.

Isolation of the infecting organism from blood cultures is presently the only method of making the diagnosis of septic shock with certainty. However, because of the rapid course and high fatality rate of the syndrome, it is imperative that the diagnosis be made and treatment instituted based on the clinical features of Gram-negative sepsis, which are strikingly similar irrespective of the etiologic agent.

Typically, in bacteremic shock a patient first presents with a chill, followed by an abrupt elevation in temperature. However, fever may be minimal or hypothermia may be present, especially in patients who are receiving steroids or immunosuppressive therapy, are elderly or are debilitated, or if profound shock is present. This is of special importance if the fever follows one to two hours after insertion, manipulation or removal of a bladder catheter or manipulation of an infected wound. Additional early features include tachypnea with respiratory alkalosis (determined by findings on studies of arterial blood gasses[94]), tachycardia, varying degrees of mental obtundation and oliguria. Less frequently seen are nausea and vomiting and occasionally bloody diarrhea.

Since the manifestations of Gram-negative sepsis are similar with all etiologic agents, it is not possible to distinguish bacteremia due to Klebsiella (as an example) from that caused by other species by clinical findings alone. However, a few unique diagnostic features occur with specific agents, such as the generalized purpura due to meningococcemia, malar hemorrhage of pregnancy due to E. coli, and ecthyma gangrenosum. Ecthyma gangrenosum is the appearance of tender, indurated or ulcerated lesions with black necrotic centers due to the invasion of the vessel wall with Pseudomonas aeruginosa. This is usually seen in patients with leukemia or agranulocytosis. Peripheral manifestations of vascular embolization may occur, ranging from conjunctival petechial hemorrhage to bullous lesions.

Laboratory features in sepsis are not extremely helpful, except for the previously mentioned early respiratory alkalosis secondary to hyperventilation. As shock continues, this will be followed by metabolic acidosis if untreated. The leukocyte count may be decreased early in sepsis instead of the usually anticipated leukocytosis, abnormal findings on liver function tests are seen in 65 per-

cent of cases and various other nonspecific laboratory abnormalities are observed. Thrombocytopenia may be observed in 50 to 60 percent of patients with septic shock but the entire syndrome of disseminated intravascular coagulation occurs in less than 5 percent.

Laboratory studies should include blood cultures, at least two sets of anaerobic and aerobic, along with Gram stain and cultures from potential sites of infection (for example, urine, lung, cerebrospinal fluid (CSF) and decubitus ulcer). Other laboratory tests should include complete blood count and studies of electrolytes, urea nitrogen and coagulation (prothrombin time, platelets, fibrinogen, partial thromboplastin time and fibrin split products) to rule out disseminated intravascular coagulation. Findings on a Gram stain of the buffy coat of the blood may sometimes identify the offending organism, particularly in meningococcemia.

In multiple studies of Gram-negative bacteremia, E. coli has been the etiologic agent in 37 percent of cases.[92] The Klebsiella-Enterobacter-Serratia group are next most common accounting for approximately 20 percent of isolates, followed by Pseudomonas and the four species of Proteus.[92] The same causes basically hold true for hospital-acquired versus non-hospital-acquired infection. Although the mortality is lower with patients in the non-hospital-acquired infection group, this is probably due to the underlying condition of the host and not necessarily the etiologic agent.

The most common portal of entry is the genitourinary tract, followed by respiratory tract, wounds and gastrointestinal tract.[93] Again, there is frequent association with manipulation or breakdown of normal host defense barriers.

TABLE II-8.—*Suggested Guidelines for Antibiotics in Septic Shock*

Infection below the diaphragm (especially bowel surgical procedures)
- Gentamicin 2.0 mg/kg iv immediately, then 1.5 mg/kg every eight hours with normal renal function; clindamycin 600 mg iv every eight hours *or* chloramphenicol 1 gm iv every six hours.

Urinary tract infection
- Ampicillin 2 to 3 gm iv every four to six hours; gentamicin iv as above.

Pelvic inflammatory disease
- If a specific organism is known, as gonococcus or clostridia, penicillin 2 to 3 million units iv every four to six hours.

Pulmonary infection
- Penicillin or clindamycin (doses as above); gentamicin (doses as above).

Bone-joint infection
- Penicillin and/or methicillin (2 to 3 gm iv every four to six hours); gentamicin

The pathophysiology of bacterial shock is incompletely understood. It is believed that endotoxin, a complex lipopolysaccharide common to the cell wall of all Gram-negative bacteria, plays a major role in initiating the hemodynamic events. Study findings suggest that circulatory and coagulation changes observed may result from complex alterations and interactions among the coagulation, fibrinolytic, kinin and complement systems. There is a redistribution and pooling of blood within the vascular bed in a manner precluding the maintenance of an adequate circulating blood volume. As a consequence of this pooling, poor oxygenation of tissues results in anaerobic metabolism, with lactic acidemia and ultimately loss of cellular integrity within vital structures. The initial hemodynamic changes appear to be a decrease in peripheral resistance, normal to increased central venous pressure and a variable cardiac output.[95]

Management and treatment of bacteremic shock is begun based necessarily on a presumptive diagnosis. Fundamental aspects of therapy include: (1) controlling the infection through use of antimicrobial agents and surgical drainage if indicated and (2) the maintenance of an effective circulating volume through the use of parenteral administered fluids or vasoactive drugs, or both. Initially, a central venous line should be placed or if available a Swan-Ganz catheter. Volume expanding fluids should be given rapidly until central venous pressure is approximately 15 cm of water or tissue perfusion is adequately maintained (stable blood pressure, adequate urine output, clear sensorium and so forth), or both. If anemia is present, blood should be used for volume expansion. The use of vasoactive drugs should be reserved for those patients in whom there is no response to volume replacement. Although there is extensive literature on a variety of agents, there is no consensus as to which drug, or which family of drugs is most efficacious. At present dopamine appears to be most promising. Adjunctive measures include administration of oxygen, correction of acidosis with bicarbonate and the use of a rapidly acting digitalis preparation in the face of persistent elevation of central venous pressure, when fluid replacement has been adequate. The use of corticosteroids still remains controversial. However, if used, the dosage should be in the range of 3 to 5 grams of hydrocortisone

or an equivalent, in divided doses, for not longer than 36 hours.

If a particular organism is suspected, the most specific antibiotic should be administered. However, as is frequently the case, the specific organism is not known and the antibiotics should be chosen with educated guesswork. If the organism is unknown, suggested guidelines (until culture findings return) are given in Table II-8. It is imperative that the dosages of the antibiotics be administered according to renal function, which often decompensates during Gram-negative sepsis. Also, whenever intravenous lines are in place at the time bacteremia or sepsis is diagnosed, they should be removed, cultured and replaced aseptically. When the blood culture findings return in 48 to 72 hours and appropriate identification and sensitivities are made, the antimicrobial regimen should be changed to the antibiotic(s) to which the organism is sensitive.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is a pathologic process due to the presence of *thrombin* in the systemic circulation. The initiation and persistence of coagulation result in the formation of fibrin, consumption of specific plasma proteins, aggregation and loss of platelets, and activation of the fibrinolytic system. The resulting effects of these processes lead to the clinical manifestations of diffuse hemorrhage or thrombus formation, or both.

Activation of Hageman factor (factor XII) is an important central mechanism in the initiation of disseminated intravascular coagulation (DIC).[96] Injury to the endothelial cell with exposure of the underlying collagen activates Hageman factor and subsequently the intrinsic clotting system. Red cells or platelet injury, or both, cause the release of phospholipid, a component needed for the proper functioning of the intrinsic and extrinsic clotting system. All act by triggering mechanisms that liberate free thrombin into circulating blood.

Thrombin has multiple actions on the coagulation system. The most important is the proteolytic cleavage of fibrinogen into fibrin monomers. During this process, smaller peptides are also produced which possess various physiologic properties. The fibrin monomers spontaneously polymerize, forming fibrin clots that are loosely bound. However, another plasma protein, fibrin stabilizing factor (factor XIII), also activated by thrombin helps stabilize the clot. Thrombin also irreversibly aggregates platelets which in effect removes them from the circulation. Finally, thrombin (and, incidentally, Hageman factor) appears to activate plasminogen directly and provides a crucial link to the fibrinolytic system.

The fibrinolysis secondary to DIC contributes to many of the clinical manifestations of DIC, especially the hemorrhagic diathesis. It has been reported that in approximately 85 percent of cases of DIC bleeding occurs and is manifest at an average of three sites per episode, with skin counting as one site.[96] Other sites of bleeding include gastrointestinal, 50 percent; wound, 44 percent; genitourinary, 31 percent, and hematomas, 27 percent. Acute dramatic bleeding occurs in approximately 75 percent of cases.[96]

Although many disease states beside infection can lead to DIC, the following are the most common infectious causes:[97]

- Gram-positive bacteria, especially pneumococcus, staphylococcus and streptococcus;
- Gram-negative bacteria (endotoxemia), especially Neisseria meningitidis, Gram-negative rods (E. coli, Klebsiella, Proteus species, Serratia, Pseudomonas, Salmonella and the like);
- Viruses, especially varicella, variola, rubella and rubeola;
- Rickettsiae—Rocky Mountain spotted fever, scrub typhus;

TABLE II-9.—*Laboratory Criteria for Disseminated Intravascular Coagulation (DIC)**

Determination	*Normal*	*No Liver Disease*	*Liver Disease*
Platelet count	250,000/mm³	≤150,000/mm³	≤50,000/mm³
Prothrombin time	12 sec	≥15 sec	≥25.0 sec
Fibrinogen	230 mg/100 ml	≤160 mg/100 ml	≤125 mg/100 ml
Partial thromboplastin time	30 sec	≥40 sec	≥60 sec
Fibrin split products (FSP)	≤1:8	≥1:16	≥1:16

Definite DIC = any 4/5 abnormal tests or any 3/5 abnormal tests plus positive FSP
Probable DIC = any 3/5 abnormal tests or any 2/5 abnormal tests plus positive FSP
Possible DIC = any 2/5 abnormal tests or 1/5 abnormal tests plus positive FSP

*Modified from Colman RW, Rubboy SJ, Minna JD: Disseminated intravascular coagulation (DIC): An approach. Am J Med 52:679-689, May 1972.

- Purpura fulminans, especially varicella and streptococcal disease, and
- Miscellaneous causes such as malaria, primarily falciparum; tuberculosis, especially miliary; kala-azar, and aspergillosis

Two syndromes warrant special mention. Clostridial sepsis can be associated with DIC especially in young women with septic abortions. Hemolysis may occur and is most likely due to Clostridia toxins or a microangiopathic hemolytic process, or both. Products of red cell lysis may lead to DIC also. A second important infection is meningococcemia. The earliest report of a hemorrhagic manifestation of this disease was the Waterhouse-Friderichsen syndrome. However, this syndrome is not always present. Patients with meningococcemia are acutely ill and febrile. Purpuric lesions or generalized petechiae are seen to develop, and hypotension and, later, renal failure may occur.

There is no test pathognomonic for DIC. The diagnosis depends upon both clinical and laboratory changes. Clinically, at least one of the following is present: blood loss from one or more sites (including petechiae), acrocyanosis or signs of peripheral vascular thrombosis, and organ dysfunction secondary to hypoperfusion or bleeding.[96]

Laboratory criteria include the measurement of the prothrombin time, partial thromboplastin time, platelet count, fibrinogen and fibrin split products. One should look at a peripheral smear to see if there are any platelets apparent and also to evaluate red blood cell morphology. The degree of laboratory abnormality will vary and depends on the severity of the process. It is helpful to separate those patients with normal liver function and those with inherent liver disease (see Table II-9) since the latter condition is often associated with abnormalities of the above mentioned coagulation measurements, making the diagnosis of DIC difficult.

The therapy for DIC is two-fold. Treatment of the underlying infection is paramount, as previously discussed. The use of heparin is controversial; however, some recent reports have shown definite improvement in clotting measurements coincident with heparin therapy.[98] Nonetheless, the final outcome of the disease may not be influenced by heparin therapy as much as by correction of the underlying process. The use of heparin is to inhibit the effects of thrombin. The dose is 100 mg per kg of body weight every four hours, or an average of 6,000 units given intravenously every four hours. The length of time of administration is determined by the response of the patient, judged both clinically and by laboratory findings. Although both the prothrombin time and the partial thromboplastin time may be influenced by administration of heparin, early signs of improvement will be shown by a fall in the prothrombin time and increase in fibrinogen. The platelet count will generally change slowly with therapy. Fibrinogen levels usually will increase in one to three days if therapy is successful.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Streptomycin	*streptomycin*
Keflin®	*cephalothin*
Vancocin®	*vancomycin*
E-mycin®, Erythrocin®, Kesso-mycin®, Ilotycin®, Robimycin®, Pediamycin®	*erythromycin*
Polycillin®, Omnipen®, Totacillin®, Amcil®, Penbritin®, Principen®	*ampicillin*
Staphcillin®	*methicillin*
Unipen®	*nafcillin*
Garamycin®	*gentamicin*
Cleocin®	*clindamycin*
Chloromycetin®	*chloramphenicol*
Kantrex®	*kanamycin*
Nebcin®	*tobramycin*
Geopen®	*carbenicillin*
Fungizone®	*amphotericin B*
INH®, Triniod®, Nydazid®	*isoniazid*
Myambutol®	*ethambutol*
Flagyl®	*metronidazole*
Aralen® phosphate	*chloroquine phosphate*
Emetine hydrochloride	*emetine hydrochloride*

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Refer to: Postmenopausal osteoporosis—Toward resolution of the dilemma—Medical Staff Conference. University of California, San Francisco. West J Med 125:137-142, Aug 1976

Medical Staff Conference

Postmenopausal Osteoporosis

Toward Resolution of the Dilemma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Of all of the disorders resulting in too litle bone, postmenopausal osteoporosis is the most prevalent. It is a very important cause of pain and disability. In the elderly it may also be indirectly a cause of death through increasing the risk of hip fractures.*

Dr. Gilbert Gordan has devoted many years to the study of osteoporosis. We are fortunate to have him here today to summarize current knowledge about that frequent and debilitating disorder.

DR. GORDAN:† Although sexually-determined bone loss is evident from paleopathologic studies of ancient bones (Armelagos,[1] Perzigian[2,3]), the relation of osteoporosis to the menopause was not clearly described until Fuller Albright made the connection in 1940.[4] The only previous suggestion of such a relationship was made by Bruns in 1882,[5] who noted that before the age of 50 hip fractures occur six times more frequently in males than in females. After the age of 50, the situation changes dramatically and for every fracture in men there are many more fractures in women. Albright also based his concept on clinical observation.

Albright made three observations leading to the concept of postmenopausal osteoporosis.[6,7] *First,* he noted that of his patients with osteoporosis almost all were women and all of these were postmenopausal. *Second,* results of balance studies carried out in these patients showed negative clacium and phosphate balances and elevated serum phosphate levels. *Third,* and very important, 1 mg of stilbestrol a day caused a reversal of all of these biochemical abnormalities. Albright also found that methyltestosterone similarly reversed the negative calcium and phosphate balances and caused nitrogen retention. He postulated that during the reproductive years sex hormones store up calcium in maternal bones for the needs of the fetal skeleton, and that loss of sex hormones at the menopause leads to bone loss. In 1968 Yendt and Gagne found that the serum calcium levels of women average 0.2 to 0.3 mg per 100 ml lower than those of men.[8] Mario Werner (then at the University of California, San Francisco) showed that serum calcium levels fall at the menarche and rise again at the menopause.[9] And Greenberg and associates showed in 1960 that serum phosphate levels rise in women after the age of 50, but do not rise in men.[10] Since estrogens inhibit bone resorption and lower serum calcium and phosphate levels, it is quite likely that during the reproductive years, estrogens restrain osteolysis, lower serum calcium and phosphate levels, and build up skeletal reservoirs of calcium.

Albright proposed an additional hypothesis re-

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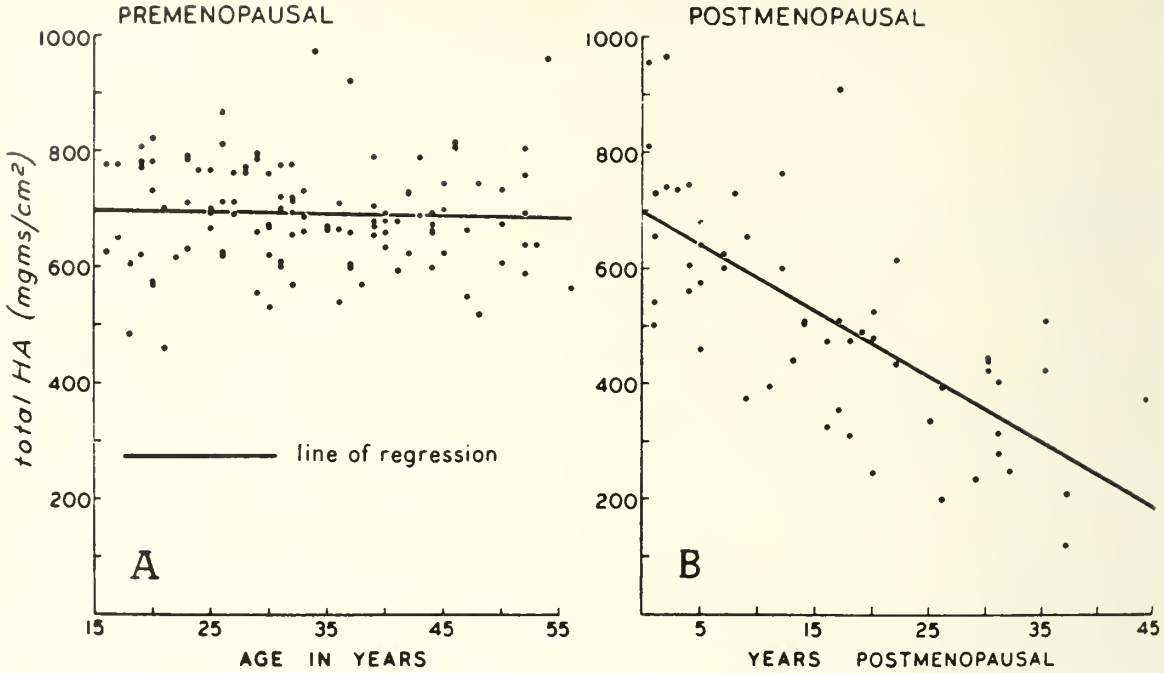

Figure 1.—Bone mineral mass of women before and after the menopause. Note maintenance of normal premenopausal bone mass in women still menstruating in their 50's. Values for young women who have been castrated are graphed according to number of years postoöphorectomy. (Reproduced with permission of Meema S and Amer J Obstet Gynecol)

garding the mechanism of action of estrogen on bone. Noting that histologic sections of bone in postmenopausal osteoporosis do not show excessive bone destruction such as one sees in osteitis fibrosa, he postulated that estrogen acts by stimulating bone formation. This thesis was supported by studies in mice and pigeons in which estrogen does indeed stimulate bone formation. This occurs to such a degree that bone actually crowds out the marrow and causes anemia but this effect is restricted to these two species. I should note at once that, while Albright's concept of the relation of the menopause to bone loss is now well documented, it now appears that in our species estrogen affects bone *not* by stimulating anabolism but by inhibiting breakdown.[11]

At this point, I think it important that we define our terms. Osteoporosis, in Albright's words, means simply "too little bone." What bone exists, is *normally* calcified. Osteoporosis is not primarily a disorder of mineral metabolism but of *bone tissue.* Too little bone can come about as a result of a number of disorders, the most common being *immobilization,* or from an *excess of catabolic adrenal or thyroid hormones,* or from *hypogonadism,* or from *alcoholism.* Osteoporosis should not be confused with other bone diseases such as osteomalacia where there is a defect in bone mineralization or osteitis fibrosa where bone is rapidly broken down by the osteolytic action of excess parathyroid hormone. In my experience, the most common problems of differential diagnosis are not osteomalacia or osteitis fibrosa but other disorders causing back pain, wedged vertebrae and radiolucency, including metastatic carcinoma, myeloma, juvenile epiphysitis, spondylolisthesis, back strains, osteogenesis imperfecta and various radiological artifacts—or no discernible bone disease at all. Hypertrophic osteoarthritis is also a common cause of back pain but is clinically and radiologically quite distinct from osteoporosis. In fact, in a current paper Dequeker finds by quantitation of bone mass that the two conditions are mutually exclusive,[12] that is to say one cannot have two much bone and too little bone at the same time.

It is now crystal clear that the osteoporoses are a group of heterogeneous disorders all having in common poverty of bone tissue. Clinically, chemically, radiologically, kinetically and—especially—in their response to treatment, the osteoporosis of Cushing's syndrome or of immobilization is quite different from the common postmenopausal type. The osteoporoses all have in common thinning of the skin, in postmenopausal osteoporosis, Cushing's syndrome, thyrotoxicosis and osteo-

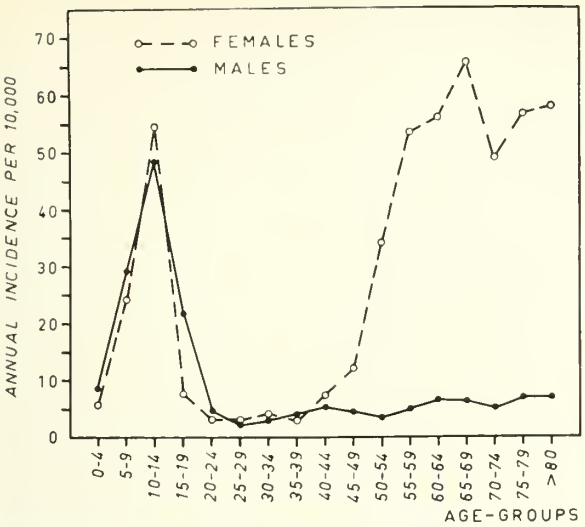

Figure 2.—Fractures of distal end of radius or ulna or both. Annual incidence in the city of Malmo. (Reproduced with permission of Alffram PA and J Bone Joint Surg[19])

genesis imperfecta. The fundamental defect in skin and bone is loss of collagen.

In the 36 years since Albright first described postmenopausal osteoporosis, considerable controversy has arisen. Some feel that osteoporosis is simply a "senile" disorder, not necessarily related to the menopause. Many have reported that osteoporosis does not respond to estrogens for no improvement is seen on x-ray studies of bone. Others have noted that while in most women with osteoporosis, back pain ceases in about three weeks, this effect is nonspecific. Still others have studied various osteoporoses by balance techniques and have noted no improvement, especially in "idiopathic osteoporosis." Recently, several prestigious investigators have actually called estrogen harmful because it reduces the rate of bone formation.

Before discussing each of these objections, I should like to register my own complaints. Many of these criticisms are based on studies of other types of osteoporosis, extrapolated to postmenopausal osteoporosis. In many cases it is not even certain that anything more than radiologic lucency was present—a subjective, nonspecific and often artefactual criterion. Much "osteoporosis" seems, unfortunately, to be in the eye of the beholder. The objections in the light of newer information have been neutralized.

We must first note confirmation by quantitative measures of sexual dimorphism in bone mass. At all ages and in all races, men have more bone than do women. There is also racial polymorphism: bone mass parallels skin pigmentation. Osteoporosis is rare in blacks and commonest in white females.[13] Women with brown or yellow skin occupy an intermediate position.[14] Two independent kinds of studies have conclusively related bone loss to loss of ovarian function. The Meemas in Toronto,[15] by elaborate and careful retrospective statistical studies, have shown that bone loss measured by cortical thickness or photon absorptiometry correlates with the menopause and not with age per se (Figure 1). This is conclusively shown in comparing young women who have been castrated with 50-year-old women who are still menstruating. In carefully controlled prospective studies of women following hysterectomy, using two methods for measuring bone mass, Aitken found that women whose ovaries are removed lose bone, while those whose ovaries are spared do not.[16] He has also shown by the double-blind technique that small doses of estrogen (mestranol, 20 μg per day) prevent this bone loss while placeboes do not.[17] In the crossover phase of this study, he even found some restoration of lost bone in women started on estrogen within three years after oöphorectomy, but none in women whose treatment was delayed for six years. Dalén and co-workers, using a different method, have also shown that women after oöphorectomy lose trabecular bone and that the bone loss occurs specifically in the three areas where postmenopausal women preferentially sustain fractures; the vertebrae, wrists and hips.[18] It has been known for many years that wrist fractures increase greatly in women but not in men after age 55 (Figure 2)[19] and the same selective increase has already been pointed out for hip fractures.[5,20] Hip fractures are of particular public health importance, accounting for considerable morbidity, hospital admissions and even mortality (Iskrant).[21]

From the data presented so far, I think it fair to say that osteoporosis occurs much more frequently in women than in men, and that the onset of osteoporosis is related temporally and causally to loss of ovarian function, either spontaneous at the menopause or surgical after oöphorectomy.

In the type of postmenopausal osteoporosis we could diagnose in the past, that is, "pathologic" osteoporosis with vertebral deformity and symptoms, as opposed to "physiologic" bone loss without clinical manifestations, we could not show restoration of bone on conventional x-ray films

following any kind of therapy. This failure to document bone increase results from the "bluntness" of our previous instruments for measuring bone mass and to the irreversability of far-advanced osteoporosis. The recent work of the Meemas and of Aitken shows that bone loss can be prevented by administration of estrogen and that bone can actually be restored if treatment is started early enough.

As to the placebo effect of estrogen on back pain, I must personally plead guilty to establishing this mechanism. In a double-blind study, evaluated by two psychiatrists, we found that estrogen relieved pain and induced well-being in 11 of 12 women with osteoporosis; but so did the psychoactive placebo dextroamphetamine-amobarbital (Dexamyl®). Even an inactive placebo (lactose) gave similar effects in about half the patients.[22] Urinary excretions of calcium and of a test load of strontium were not altered by the two placeboes but were both reduced by estrogen. In another group of patients treated with fluoxymesterone, there also was retention of calcium and strontium but there was no relief of back pain. The test period was only six weeks. It is uncertain whether placeboes would give sustained relief of pain and improved well-being as long as estrogens do. It is also possible that the androgen might have produced better results if administration was continued longer. In any event, I am pleased that women feel better during estrogen therapy but I do not take relief of pain per se as evidence that estrogens affect osteoporosis.

Perhaps the most cogent current question is whether estrogens produce a harmful lowering of the rate of bone formation. In 1963, Dr. Eisenberg and I showed that estrogens, androgens and anabolic agents (all really weak androgens), while inducing positive calcium balance, actually lower the bone accretion rate (as measured by bone-seeking tracers).[23] These findings have been widely confirmed and lead to the conclusion that these agents act, not by stimulating bone formation, but by inhibiting bone breakdown. I suppose accretion falls because of the internal homeostasis of bone where accretion and resorption are necessarily normally coupled. As a corollary, in advanced osteoporosis, one should not expect to see much new bone formation but only a cessation of the destructive process. This, of course, is locking the stable door after the horse is gone. I was very pleased in 1969 when Jenifer Jowsey's microradiography confirmed our findings by showing a reduction of bone resorption surface in biopsy specimens from women receiving conjugated estrogens (Premarin®), 2.5 mg a day.[24] But in 1972, she and Riggs reported that the amount of bone formation surface dropped to one eighth of the bone resorption surface on long-term estrogen treatment.[25] This brings up some interesting points on "quantitative" microradiography. This technique requires a bone biopsy specimen and quantitation of those surfaces where formation and resorption appear to be taking place. At best this gives an area, *but an area is not a rate.* Conflicting results have been reported. In Minnesota, postmenopausal osteoporosis is associated with normal formation and excessive resorption; in Paris, resorption is normal and formation decreased.[26] There may be technical reasons for these differences, but I think it clear that microradiography is a very tricky technique. Does estrogen harm bone? I think the clinical information to the contrary is more illuminating and less controversial.

Between 1948 and 1955 I started a prospective study on 220 women with postmenopausal osteoporosis to compare estrogens with androgens and anabolic agents.[27] Most of the anabolic agents were chemical derivatives of testosterone whose anabolic activity had been identified by growth of the levator ani muscle. Since the genital effects of estrogens and androgens are undoubted drawbacks, I hoped that anabolic agents with less genital activity would be the answer to a maiden's prayer. Unfortunately, in a long-term treatment the androgenic activity of such anabolic agents was poorly tolerated by postmenopausal women. They also appeared to be far less effective in preventing fractures than were the estrogens. As a result, there was a change to estrogen therapy in almost all women in this study.

Now, 28 years later, we still have 24 of the original 220 women taking estrogens. They came to us originally for very advanced osteoporosis with vertebral fractures and considerable loss of bone. Today they are up and around in their usual activities and fractures are no longer occurring. If estrogens had reduced the bone formation rate to one eighth that of resorption, these women should have no bone at all. Therefore, I am unable to agree that estrogens exert a detrimental effect on bone. In support of our observations it has recently been shown by the use of radiocalcium kinetics that in untreated postmenopausal women there are statistically significant

deviations from the premenopausal norm in that bone resorption exceeds bone formation.[28] In 25 women given estrogens the kinetic aberrations which lead to bone loss and postmenopausal osteoporosis did not occur. I think it is therefore clear that the postmenopausal changes leading to bone loss are preventable and that "senile" osteoporosis of women, like "senile" vaginitis, is not the inevitable consequence of aging but the result of hormone deficiency. This is totally preventable by small dose estrogen prophylaxis.

Recently considerable attention has been given to the possibility of increased risk among estrogen treated patients for the development of uterine cancer.[29,30] This disorder is heralded by vaginal bleeding and is treatable if caught at an early phase. We have handled this as follows: Whenever breakthrough bleeding occurred, except at the time of withdrawal of estrogen, the patient was referred to her gynecologist, and usually a dilation and curettage (D and C) was carried out. Today either aspiration biopsy study or other simple office procedures (such as jet-wash) without general anesthesia may be utilized effectively for diagnostic purposes to rule out early endometrial neoplasia. In 4 percent of our patients there were endometria that were so sensitive to estrogenic stimulation that the problem of repeated breakthrough bleeding was particularly troublesome and could not be controlled by converting the endometrium with a progestational steroid.

After several D and C's showing only benign endometrial hyperplasia, it is tempting to assume that subsequent episodes of bleeding at times other than following withdrawal of estrogen are also of benign origin. Our experience leads us to the opposite conclusion. All such episodes must be thoroughly investigated since we have encountered three cases of endometrial carcinoma in our 220 estrogen-treated women. These occurred at the 8th to 16th years of estrogen therapy. The peak incidence of endometrial cancer, at ages 60 to 64, has remained constant in this country at 80 per 100,000 women per year as measured in the Second and Third National Cancer Surveys (1947-1948 and 1969-1971). At that rate, we should have seen one or two cases. Actually we saw three, not significantly different in this small series of 220 osteoporotic women. Of course, every case of endometrial cancer is of concern despite the low mortality in this disease and the fact that it is a rare cause of death in this country (2,252 deaths in 1974). Since the endometrium is an estrogen-sensitive tissue, a possible relation between estrogens and endometrial cancer has often been suspected (Gusberg, 1975).[31] In 1975, Smith and co-workers and Ziel and Finkle reported an increased use of exogenous estrogens in women with endometrial cancer. These data undoubtedly reflect increased detection, probably because estrogens cause uterine bleeding which in turn leads to microscopic examination of the endometrium and therefore to early detection of endometrial carcinoma. In a study where this factor was controlled, Dun and Bradbury[32] and Pacheco and Kempers[33] found estrogen usage equal in women with endometrial carcinoma and women simultaneously admitted for postmenopausal bleeding from benign endometrial causes. There is no evidence of increased mortality from endometrial carcinoma. In fact, Cramer, Cutler and Christine[34] (1975) of the National Cancer Institute report that mortality is actually decreasing. Nonetheless, every case of bleeding-not-according-to-plan requires complete gynecologic investigation with histologic examination of the endometrium. Estrogen-induced endometrial hyperplasia and bleeding will predictably increase the detection of early endometrial carcinoma and should thereby reduce mortality, just as the Papanicolaou smear did for cervical cancer.

This year, Fuller Albright would have been 76 years old. He was a uniquely original thinker, a superb clinician, an intuitive investigator, a delightful person and a good friend. It gives me particular pleasure to conclude today's presentation by summarizing recent evidence supporting his basic concept of the central role of estrogens in postmenopausal osteoporosis.

First: loss of ovarian function is rapidly followed by loss of bone.

Second: small prophylactic doses of estrogen prevent this bone loss.

Third: menopausal women who have already lost enough bone to cause deformity, fractures, loss of height and invalidism, cease having fracture and losing height when given estrogen replacement therapy.

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Important Advances in Clinical Medicine

Epitomes of Progress—Plastic Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Plastic Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Plastic Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Removal of Commercial Tattoos of the Skin

UNTIL RECENTLY, tattoos were removed in one of five ways: (1) full-thickness excision of small tattoos, with undermining and suture closure; (2) full-thickness excision of larger tattoos, with skin grafting for closure; (3) partial-thickness excision (cutting off a split-skin graft of the area); (4) partial-thickness removal by dermabrasion; (5) partial-thickness peeling and sloughing, induced by tattooing with tannic acid paste or use of some other irritant.

Full-thickness excision is still best for small tattoos. Skin grafting for the large ones may, however, result in mismatched skin patches with border scars. On the whole, the partial-thickness removals were good for making an obscene picture or word indistinguishable, but left scattered deeper portions of the pigment visible.

In 1974, Manchester introduced superficial abrasion of tattoos followed by the rubbing in of table salt. A considerable inflammatory reaction occurred, followed in ten days by separation of an eschar containing most, but not all, of the pigment. By repeating this it was possible to remove all the pigment.

In 1975, Clabaugh reported superficial dermabrasion of tattoos, followed by application of 2 percent gentian violet, followed two days later by daily compresses of 0.25 percent acetic acid for one hour, with dressings of antibiotic ointment in the intervening periods. Secondary spot abrasions were required in some cases, but the results were generally quite dramatic. The combination seemed to induce migration of pigment to the surface (possibly in phagocytes), once that surface was opened and was kept open.

Self-induced india ink tattoos are usually deeper and are better treated by surgical excision.

FRANK MCDOWELL, MD

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Face Lifting Operations in Men

As a result of increased acceptance by men of surgical operations for cosmetic purposes, more and more face lifting operations are being done. This procedure now is done on men from all walks of life, from executives to laborers. Most of these patients are over 40 years old. Many are balding. This is where ecology comes into play. In usual face lifting operations a portion of the scalp is discarded when the facial tissues are lifted. Instead of discarding this hair-bearing tissue, it can be used for donor plugs or strips in the hair transplant process. This eliminates the necessity for removing the donor plugs from the back of the head—a process almost as time consuming as the face lift itself. This combined procedure has been well accepted by many men.

Frederick Grazer, MD

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Continuous Compression Treatment of Hemangiomata

Most hemangiomata on the skin of newborn children will resolve or regress significantly by the second year of life. In a smaller proportion of these congenital tumors, aggressive treatment may be required because of their location (such as the neck) or complicating factors (such as anemia due to blood sequestration). Most of these lesions are enlarging masses that discolor and distort the skin wherever they are present. They are understandably a very distressing problem for parents who are reluctant to accept temporizing treatment.

In 1964, Moore reported the successful treatment of a patient with a giant hemangioma by a pressure technique. This technique, readily applied to congenital enlarging hemangiomas on the extremities and most of those on the trunk, can be accomplished with the use of an elastic compression bandage applied and changed by the parents three times a day.

In one of the author's cases, a massive hemangioma involving the foot up to the knee was successfully treated to complete resolution in less than eight months. The compression treatment could logically be extended to treat and thus hasten resolution of some of the more troublesome and frequently occurring tumors on the head and perineum.

The mechanism of action of the compression treatment is the stasis and ultimate thrombosis of the extensive serpentine labyrinth of small blood vessels.

Donald J. Mangus, MD

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Breast Reconstruction After Radical Mastectomy

Breast reconstruction following radical mastectomy has become an accepted procedure during the past few years. Even the most conservative surgeons are allowing their patients to have reconstructive procedures done. It is now considered that these operative procedures do not alter patients' ultimate survival rate.

Approximately 70,000 mastectomies are done every year but not all patients are suitable candidates for a reconstructive procedure. The most important consideration is curing the patient of her tumor. However, many women are not satisfied to go through the remainder of their life with the resultant deformity. From the reconstructive surgeon's standpoint, a woman who has had a modified radical mastectomy is a better candidate for reconstruction than someone who has had the classical radical mastectomy with the removal of all of the pectoralis muscles.

Before any reconstructive procedure is undertaken, the patient's expectations must be carefully determined by the reconstructive surgeon. It should be emphasized that a perfect cosmetic result cannot be obtained; most women, however, do not expect it, they only wish to be able to lead normal lives and wear clothes in a normal manner.

The most common technique used is the reconstruction of the mastectomized breast using a silicon prothesis. This reproduces the contour in the area of the operation. In addition, some patients often wish further reconstruction to form a semblance of an areola and a nipple. This can be done either by using a portion of the opposite nipple and areola or using a labia minora graft. If the remaining breast is small and there is no evidence of any pathological process, either on

physical examination or on mammography or xerography, no operation is indicated on the opposite breast. If the opposite breast is large or if it is involved with some pathological process, the treatment may be carried out in various ways. Such techniques as subcutaneous mastectomy; simple mastectomy; and reduction mammoplasty have been used; however, a comprehensive discussion of the indications for the operation cannot be covered in an article of this type. Most plastic surgeons today do not use large flap procedures to reconstruct a breast since these leave large scars in other areas and the results are not the most cosmetically acceptable.

In summary, breast reconstruction following mastectomy is an acceptable procedure in properly selected candidates. After careful examination and selection, many women who in the past were forced to spend the rest of their lives with the physical and psychological deformity of a mastectomy may have this problem resolved by rconstructive surgical procedures.

EUGENE W. WORTON, MD

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Newer Aspects of Microvascular Tissue Transfer

THE CLINICAL TRANSFER of tissue by microvascular techniques has become much more frequently used in the past few years. Free flaps of a number of different varieties have been transplanted from the chest to the face or extremities and from the groin to the extremities or head and neck areas. Bone grafts utilizing the ribs and the fibula have been used in microvascular surgical procedures to bridge unstable fractures of the extremities, thus providing good, prompt, boney union in difficult problems.

As with all new techniques, complications have developed in the transplantation of such tissues. These are reported to occur in from 10 to 30 percent of cases, depending upon the experience of those reporting.

HARRY J. BUNCKE, MD

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Surgical Procedures on Hands

CONTINUING DEVELOPMENT of microsurgical technique and instrumentation has permitted dramatic recent advances in surgical procedures on hands. Hand replantation should not, however, overshadow the increased emphasis on atraumatic technique, on the use of fine suture materials, and on the principles of wound healing.

From the first tentative laboratory work a decade ago, we now have sutures 18 to 22 micra in diameter, needles 50 to 70 micra in diameter and versatile quadrascopes that allow the suture of vessels 1 mm and less with a greater than 90 percent patency rate.

The replantation of amputated digits, hands, feet and upper extremities is now a well established operation. In many clinics there has been an 80 percent success rate, which reflects careful selection as well as superior techniques. Although the precise indications for replantation are still being developed, patients with amputations of multiple digits, thumbs, entire hands and upper extremities are candidates for replantation. The nature of the injury, age, general condition and occupation of the patient are important in the decision of whether to attempt replantation.

Physicians likely to see patients with amputations should become familiar with the care of the amputated part and the institutions and personnel with replantation capability. Not all amputations are suitable for replantation, but the referral should be made to a microvascular surgeon for evaluation.

Nerve repair and reconstruction has similarly benefited from the emphasis on the biologic aspects of wound healing. Scar tissue interposed between sutured nerve ends is the main deterrent to nerve regeneration. The two major contributors to scar tissue in a nerve repair are tension and crude technique. Millesi has made a significant contribution to peripheral nerve surgical procedures by emphasizing interfascicular nerve grafts. Multiple sections of donor nerve, usually the sural nerve, are sutured to individual fascicles of the injured nerve with 10-0 nylon using the operating microscope. This detailed placement of a nerve graft enhances the chances for the regenerating axon to grow into the collapsed Schwann sheaths. After 12 to 24 months, most denervated muscles are too fibrotic to become functional following renervation; however, the equally important sensibility can be reestablished

even after many years of denervation. This increased emphasis on atraumatic technique has led most hand surgeons to carry out even routine neurorrhaphy with magnification.

Providing skin and soft tissue coverage for the mutilating type of hand injury has also benefited from the advances in microsurgery. A free flap can be taken from the groin and transferred in one stage to the hand with microvascular anastomosis of the arteries and veins. The traditional multistaged flap coverage of soft tissue defects has also been refined so that larger areas can be resurfaced with thin supple flap tissue.

The final area that should be mentioned is the continuing development in prosthetic finger joint replacement. At present, prosthetic devices are available for proximal interphalangeal joints, metacarpalphalangeal and lunate, scaphoid and trapezium. These devices are durable, reasonably complication free, and can allow a previously painful, nearly useless hand to function without pain.

JOHN J. SILSBY, MD

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Resection Surgical Operation of the Head and Neck Region

RENEWED INTEREST in combined drug therapy has encouraged surgeons to undertake major resection of squamous cell cancer of the head and neck region for palliation as well as for potential curative resections in extensive lesions. Although the basic concepts of managing cancer of the head and neck region have not changed in the last decade, there is now a trend to have such management geared more to the individual patient in the regional dissection of lymph glands and the more aggressive use of irradiation in conjunction with surgical operation. Improved concepts and techniques in reconstructive surgical procedures have permitted extensive operative procedures for resection and reconstruction with minimum loss of function. Although the numbers of patients presenting with primary cancer of the head and neck region are diminishing, it is a continuing problem and the functional disability that tumors of the head and neck region present remain a critical aspect of this disease. The low five-year survival from tumors of the head and neck region was in some ways a function of the reluctance on the part of the treating surgeon to adequately resect lesions about the face. Improved techniques now allow more extensive resections and it appears that the five-year survival rate is gradually improving. This improvement is not dramatic and it is hoped that improved concepts in drug therapy and immune therapy will further enhance the treating physician's ability to control cancer of the head and neck.

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Laser Management of Cutaneous Vascular Lesions

THE ARGON PHOTOCOAGULATING LASER has been used for five years to treat cutaneous vascular anomalies of the skin such as port-wine stains, capillary and cavernous hemangiomas, telangiectasia and superficial varicosities of the legs. The most satisfactory results have been with port-wine stains, or nevus flammeus, a congenital vascular lesion, red or purple in color, often causing significant facial deformity. Previous treatment methods such as excision and grafting, dermabrasion and tattooing have been relatively unsatisfactory.

Argon laser light is very intense, may be finely focused, and is selectively absorbed by the red pigment in the hemoglobin molecule. When used to treat a port-wine stain, the laser beam passes through the intact skin, sparing secondary skin appendages. As the beam encounters the hemangioma's red pigment, it releases its energy as heat, causing coagulation and vessel thrombosis. The lesion is thereby substantially obliterated, but the overlying skin is relatively unharmed, so that the laser burn may heal with minimal scarring. In our experience with more than 40 patients, this treatment has resulted in two scars, and these are becoming less distinct with maturity. Histopathologic examination of treated tissues shows minimal increase in dermal collagen and decreased numbers of blood vessels, with intact secondary skin appendages. Furthermore, laser light does not appear to produce the ionizing changes seen with x-radiation.

Use of an argon photocoagulating laser shows

promise as a satisfactory treatment for disfiguring port-wine stains. Continued research will help to define the role to be played by this exciting form of radiant energy.

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The Present Status of Dermabrasion

DERMABRASION or surgical planing is a technique that consists of removing the epidermis and a portion of the dermis, while preserving the adenexa in sufficient numbers to allow spontaneous re-epithelialization. The technique continues to be a very useful tool in the armamentarium of the plastic surgeon and dermatologist.

The purpose of surgical planing is to smooth surface irregularities of the skin. Its primary use continues to be in the treatment of scars and pits caused by acne, chicken pox and smallpox. Abrasion can also be a beneficial adjunct in the treatment of traumatic scars, foreign bodies, amateur tattoos and fine wrinkles especially of the cheek and forehead. Some benign tumors, such as keratoses, may also be treated by this method.

Surgical planing is done with a high speed rotary abrasive instrument under general or local anesthesia.

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Treatment of Melanoma

IN TREATING MELANOMA it now appears that the thickness of the tumor may be of even greater significance in determining the need for lymphadenectomy than the anatomic level of skin invasion (Clark's levels). Although the importance of the inflammatory cell infiltrate is still being evaluated, its presence appears to be a favorable sign. While the cell type may also be significant, this factor is understood even less well.

Surgical removal of regional lymph nodes is highly significant in determining the prognosis; it is especially so in thick tumors or those with extensions to levels IV and V.

Immunotherapy with bacillus Calmette-Guerin (BCG) and transfer factors should be considered experimental. Chemotherapy with dimethyl triazeno imidazole carboxamide (DTIC) or other drug combinations are available for late stage disease, though the results of treatment have been disappointing.

Urine chromatography may detect melanogens from liver metastasis three to four months before such findings are shown on liver scanning.

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EDITORIALS

A BICENTENNIAL EDITORIAL

Medical Care as a Social Enterprise

IT IS OFTEN OVERLOOKED that medicine is primarily a social profession and medical care is a social enterprise. This is true of interactions with patients and other health professionals, or with representatives of the community or of the public. In these interactions physicians have often spoken or acted with something approaching Olympian authority, and some still do. But the ground rules are changing. "Doctor's orders" are now tempered by "informed consent." A majority of "consumers" is now empowered by law to make many crucial health care decisions where professionals used to make them. And the traditional domain of medicine is being further assaulted as other health professionals can and are being trained to carry out a surprising number of functions that traditionally have been the sole province of physicians. Each of these trends places much of what has been the responsibility of medicine in other hands, and if the caring, curing, preventing and decision-making fall more and more to others, what will be the future of physicians and the medical profession, and how should the profession prepare for it?

Instinctively one senses there is a role for the medical profession which will remain essential and valid as this socialization of medical and health care proceeds and the role and responsibility of other professionals and nonprofessionals increases. There surely is a function that only medicine and physicians can do. It is suggested that this be identified, and that it is to be found in two unique strengths of medicine within the social enterprise. First, medicine is the only professional discipline concerned with the individual person as a whole; with the state of health, well-being and quality of life of the person, and with the obverse—any illness, injury or emotional disturbance in the person. Second, and a corollary to this, physicians are society's designated professional authorities for personal health and its disorders; for advising what is wrong, what is likely to happen and what can be done about it, and for advice and often direct action in the prevention and treatment of ill health and the restoration and maintenance of health. This places physicians and the medical profession in an authoritative position at the focal point of the whole social enterprise—where it succeeds or fails, where health, well-being and quality of life are or are not achieved by the individual person. This will be of growing importance as the social quest for achieving these for everyone gathers further support and momentum. This function of physicians and of the medical profession remains constant in the changing social milieu. All that changes is the way the function is best carried out in practice.

Since authoritative decision making by physicians is no longer considered to be all that de rigueur, the problem becomes more to make professional help available to the decision makers so that their judgments will be informed; that is, to see that the knowledge and experience of medicine are fully brought to bear as the decision is made. The process for accomplishing this is clearly a social process and foreshadows a role of physicians acting more as partners in a social enterprise for patient care and health care. Physicians will be working as partners with patients, other health professionals, community representatives and the public, and more as advisors than as dictators of what ought to be done. Once the decision is made, a physician may be called upon to help carry out the decision as a manager, a consultant, or as a skilled technician as in surgery for instance.

This will require a new emphasis on what has been an old approach. Physicians have always acted as advisors and teachers. But the new emphasis will require that this approach become more visible and more established than has been the case. Also it will require refining some old tools and developing some new ones. It is suggested that most of the tools and skills that will be needed are the same ones a physician needs today, but does not always have—tools that may

presently lie outside the technical skills of each specialty but are needed for effective social action as professional partners in medical and health care.

Among the skills and tools that will be needed are sound training in the overall capabilities and limitations of the art and science of medicine as these relate to health, well-being and quality of life—and their disorders; direct experience as "partners" in social interactions with other health professionals, community representatives and the public in social enterprises for medical care and health, and definite professional skills as problem solver, manager, teacher, advocate and skilled technician in the changing social milieu of professional practice. It is likely that some changes in forms of practice, medical education and even research will be required and physicians should be in the forefront of planning and bringing about these and whatever other changes may be needed.

— MSMW

Estrogens and Osteoporosis

THE FIELD OF metabolic bone disease is rife with semantic ambiguity. The term "postmenopausal osteoporosis" is an example. It is used interchangeably to designate (1) age-related, sex-specific bone loss in women after menopause, (2) a condition of bone fragility with fracture in postmenopausal women, defined as consisting of a quantitative reduction in qualitatively normal bone and (3) the vertebral crush fracture syndrome common in postmenopausal women in which abnormalities of osteoblast function and osteoid mineralization are sometimes shown on bone biopsy studies. The extent to which these three conditions coincide remains to be established, and for the moment it appears that they may be substantially divergent.

In the Medical Staff Conference elsewhere in this issue of the WESTERN JOURNAL, Gordan defends the use of estrogen treatment in postmenopausal women with the crush fracture syndrome, citing both his own experience with such patients (which is relevant) and the work of others using estrogen to retard age-related bone loss (which may not be relevant). Further, the designation of such patients as "osteoporotic" itself creates a problem, for if we define osteoporosis to exclude qualitative abnormality of bone, how do we handle the abnormalities observed on biopsy studies in patients otherwise typically "osteoporotic"? It will not do to shunt such patients into another ambiguous category such as osteomalacia, for they may fit there even less well. Our definitions have, it seems, gotten ahead of our observations. This entire cluster of conditions needs a thorough restudy and reclassification, and until that is accomplished we are forced to deal primarily at a phenomenological level.

What can be said, therefore, of the *phenomena* discussed by Gordan and associates: the physiologic effects of estrogens on bone and the therapeutic effects of estrogen in the crush fracture syndrome?

It is now well-established that the sex-specific loss of bone with age is related to estrogen withdrawal at menopause and that this loss can be prevented by estrogen replacement. At least this is true for the more easily measured bones of the hand and forearm. Estrogens suppress bone remodeling, resorption first, then later formation also. They appear to act by partially inhibiting the parathyroid-mediated first steps in the cellular resorption cycle. Thus the positive balance effect of estrogens is accompanied by divergent changes in bone resorption and in immunoreactive parathyroid hormone (IPTH) levels, and is in fact caused by those changes. In 1965 I postulated that much of the age-related bone loss in women was a specifically parathyroprivic phenomenon, caused in part by estrogen withdrawal.[1] Consistent with this prediction it has subsequently been found that levels of IPTH are depressed in untreated postmenopausal women and are elevated to premenopausal levels by estrogen, and more recently that low dosage parathyroid hormone (PTH) treatment in osteoporotic women has a calcium anabolic effect.[2]

We have recently observed an additional link between estrogen and calcium metabolism in postmenopausal women.[3] Calcium balance performance on any given calcium intake deteriorates after menopause, and this change, too, can be abolished by estrogen. It is intestinal absorptive efficiency that is specifically decreased after menopause, not the utilization of absorbed calcium. Although a specific action of estrogen on vitamin D metabolism has not been excluded, this effect can be satisfactorily explained by the induced changes in PTH secretion.

Therefore, from all available evidence postmenopausal bone loss is related to estrogen withdrawal and can be prevented by estrogen treatment. But it is not certain what this means for the vertebral crush fracture syndrome, or whether experience with prevention of peripheral bone loss can be extrapolated to treatment of spine and hip fractures. Gordan is quite right in focusing on fracture rate as the important criterion in evaluating efficacy of estrogen treatment, and he cites, in results reported elsewhere,[4] a remarkable reduction in fracture rate following start of therapy. Other clinicians working with estrogen in such women have not had such good experience.[5] And indeed it would be surprising if they had, for compression fractures must be the result of *prior* bone loss. The prevention of further loss may reasonably be expected from estrogen treatment, but a dramatic cessation of fracturing seems too much to expect. Many observers find that patients tend to stabilize spontaneously after a few compression fractures, with or without treatment. Hence future studies will certainly require better untreated controls than have been available in any of the results reported to date.

Finally, what of safety? I quite agree with Gordan that estrogens do not harm the osteoporotic skeleton. How much they help is perhaps less certain, but they certainly do not harm bone. Endometrial cancer is quite another matter. The morbidity of spine and hip fractures seems sufficiently great to justify the small risk of increased endometrial cancer associated with estrogen, if it could be securely established that estrogens were an effective preventive measure. Hence, at a phenomenological level, long-term, well-controlled studies still need to be done, both in treatment of crush fracture patients and in defining the relationship, if any, between estrogen effects on age-related bone loss and the prevention of crush fractures.

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Colonic Polyps and Carcinoma

THE ROLE OF epithelial polyps in the pathogenesis of carcinoma of the colon continues to be controversial. Basil Morson has been instrumental in defining the natural history and histopathology of colonic epithelial polyps and in resolving some of the controversy regarding the polyp-cancer sequence hypothesis. Much of the previous confusion relates to disagreement regarding histopathologic appearances of epithelial polyps and their potential for malignant transformation. In the article by Morson appearing in this issue of the WESTERN JOURNAL, these points are reviewed and clarified. Some authors may still contend that most colon carcinomas arise de novo from colonic mucosa and not from benign epithelial polyps.

It is now clear that there are four distinct histologic types of epithelial polyps of the colon: (1) hyperplastic (metaplastic), (2) adenomatous (tubular, glandular), (3) mixed type (papillary, villoglandular, tubulovillous) and (4) villous adenoma. Hyperplastic polyps are very common and appear as tiny, smooth "mammilations" at time of proctosigmoidoscopic or colonoscopic examinations. These lesions have only a minor imbalance in the cycle of cell renewal and release,[1-3] with minimal excess cellular production (hyperplasia). A slight expansion in the zone of cell division occurs but complete differentiation into goblet and absorptive cells is maintained. These polyps are not neoplastic and have no apparent malignant potential.[1-3] On the other hand, in adenomatous, mixed or villous polyps the zone of cellular proliferation, which is normally restricted to the lower portion of the colonic crypts, is expanded and deoxyribonucleic acid (DNA) synthesis is not repressed.[4] This leads to a prolonged DNA synthetic phase (prolonged S-phase). As these proliferative lesions progress, the cells develop properties that enable them to be retained in the mucosa in increasing numbers leading to the formation of polypoid structures.[4] The malignant potential of these lesions is associated with the predominant histologic appearance of the

lesions as they enlarge. When the histologic appearance of the polyp is that of a villous adenoma, the likelihood of the polyp containing foci of invasive adenocarcinoma is high. Detection of foci of invasive carcinoma within the villous adenomas depends on the number of sections examined by the pathologist after resection of these lesions. The nature of the growth of villous structures may also influence the frequency of appearance of metastatic or invasive carcinoma. These lesions tend to remain sessile enabling the foci of invasive carcinoma to reach the submucosa and muscularis mucosa early in the natural history of this neoplasm.[2,3] The malignant cells will then have ready access to lymphatics in the muscularis mucosa, the normal route for metastatic spread of large bowel cancer.

Adenomatous (glandular tubular) polypoid lesions may give rise to malignant leisons of the bowel but at a reduced frequency when compared with villous adenomas. To a large extent this notably reduced potential, as well as a tendency in the past to include hyperplastic polyps in the same category as adenomatous polyps, is the source of much of the controversy. As Morson indicates, the common adenomatous polyp is usually small and rarely contains invasive cancer. Investigations[5,6] on adenomatous polyps have defined a histologic spectrum of adenomatous polyps which ranges from well differentiated to poorly differentiated lesions containing foci of severe dysplasia (carcinoma *in situ*). The findings in these studies suggest that well differentiated adenomatous polyps are stable whereas those containing dysplasia are more likely to become invasive malignancies. Kalus[7] showed in organ tissue cultures that more than two thirds of the adenomatous polyps cultured underwent morphologic transition from cytologically benign adenomatous polyps to focal carcinoma *in situ*. Moreover, a few polyps developed invasive features similar to those observed in organ-tissue cultures of colonic adenocarcinoma. Another feature of adenomaotus polyps which may contribute to the reduced incidence of invasive malignancies relates to the tendency of these polyps to become pedunculated. As the glandular head of the polyp is drawn away from the mucosa, the lymphatics are left behind in the muscularis mucosa, reducing the chance for malignant cells to reach the lymphatic channels.[3]

Polyps containing both glandular and villous structures have an intermediate malignant potential as compared with pure glandular or villous tumors. This is related to the presence of villous pattern and the increased size of these lesions. Previous controversy regarding malignant potential of adenomatous polyps probably relates in part to this category of lesions which in the past may have been confused with either pure glandular or pure villous adenomas. Results of several studies[5,6] have shown that larger polyps are more likely to have areas of severe dysplasia, villous structures or invasive carcinoma. However, even small villous adenomas have a high risk of containing foci of invasive carcinoma.

The aforementioned evidence does not refute observations that some polypoid structures, regardless of size, are polypoid carcinomas that do not originate from benign epithelial polyps. Many polypoid carcinomas are small, contain no remnants of benign tissue and, therefore, support the concept that carcinoma can arise de novo from colonic epithelium without the intermediary adenomatous polyp phase. Patients with adenocarcinoma of the colon, however, are likely to have epithelial polyps elsewhere in the colon. In patients with polyps, additional polyps are more likely to develop and there is a higher risk of colonic adenocarcinoma developing than in persons without polyps. This suggests that the intraluminal or host factors—or both—which induce neoplasia in the colon affect the entire colonic epithelium leading to either benign neoplastic polyps or adenocarcinoma.

Although the controversy regarding the malignant potential of adenomatous and villous polyps of the colon will probably continue, it should not alter the clinical approach to these lesions, particularly since introduction of fiberoptic colonoscopy. This instrument has improved the accuracy of diagnosis of colonic lesions and simplified removal of polyps. Before the introduction of fiberoptic colonoscopy, the decision to remove a polyp that was beyond range of the proctoscope meant a major surgical procedure. In skilled hands the fiberoptic colonoscope has reduced the morbidity and mortality of polypectomy to a very acceptable level even in elderly persons with other medical diseases.

Wolff and Shinya[8] reported their experience of endoscopic removal of more than 2,000 polyps. There were no deaths and only one complication requiring operative intervention. They state that laparotomy is now reserved for polyps not suitable for endoscopic resection or where a question of

residual cancer exists. They emphasize the need for proper orientation of the excised polyp before sectioning in order to distinguish superficial areas of atypia from foci of invasive carcinoma extending into the submucosa. They recommend abdominal exploration for "polypoid carcinomas" and broad, flat lesions showing invasive cancer. If a polyp has foci of invasive carcinomas but has a long stalk with no evidence of lymphatic permeation into the stalk, leaving a zone of clearance between the level of maximal tumor penetration and the plane of cautery resection, they recommend follow-up examinations of the patient with periodic colonoscopy. The basis for conservative management relates to 12 of their patients in this category in whom abdominal exploration was carried out, and no residual cancer was detected. As a result, they now reexamine the area of previous polypectomy by colonoscopy at appropriate intervals rather than proceeding with a laparotomy and segmental resection in this group of patients. A larger series of patients managed in this fashion is required to establish this as the appropriate approach.

Developments in radiologic techniques using double contrast techniques have improved the radiologic detection of colonic polyps. This approach in combination with colonoscopy provides a more reliable approach for early detection of polypoid lesions of the colon. As these techniques become more widely used and neoplastic lesions removed from the colon at an earlier time, perhaps we will see a reduction in the mortality from carcinoma of the colon.

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An Awesome Force in Government

It is suggested that governmental bureaucracy, particularly the federal bureaucracy, is becoming an awesome force in government which is beginning to affect and in some instances to control the lives of Americans. In a way this is a natural result of the growing interdependence of modern society and the growing complexity of government. But most notably at the federal level the bureaucracy is beginning to develop an authority of its own capable of influencing both the executive and legislative branches of government in important ways, and even making them significantly dependent upon it for information and advice, and thus to a significant extent these elected officials become responsive to it. This can be and is rapidly becoming a source of awesome power. It makes it possible to influence the laws that are passed, and then by writing regulations which have the full effect of law, to control the manner and extent to which the laws are implemented. All too often the elected officials find themselves at an extraordinary disadvantage and curiously impotent when it comes to bringing about any change which is not desired or approved by the bureaucracy.

As seems to be the case so often these days, medicine and health care find themselves at the interface where the need for some regulation of a complex and interdependent social, economic and political system confronts the rights of citizens to individual freedom and personal fulfillment. These rights, under our system, the government is supposed to protect. Government therefore is actually found to be in a kind of conflict of interest, and at the moment the regulators seem to have the upper hand in the health care field at least. In theory our system of representative government and the judiciary should strike a balance and to the extent possible achieve both goals. It is possible that this may yet be accomplished. But the awesome growth and strength of the governmental bureaucracy was not anticipated and so

far there has been no adequate provision to make it effectively accountable to anyone or anything outside of itself for its actions.

As governmental involvement—some call it intrusion—in medicine and health care has increased over the years, medicine has sought recourse first with the executive and then with the legislative branches of the government, in the belief that they could or would act. And now the profession finds it necessary to turn more toward seeking relief through the courts—a costly, cumbersome and time-consuming process. It is surely time to develop some better method of accountability for the regulatory and often arbitrary powers of governmental bureaucracies, and for some more attention to be paid to the rights and interests of the citizens who are regulated. There are bills addressing these problems in both houses of the Congress (such as HR 12048, sponsored by Representative Walter Flowers of Alabama) and they deserve the support of the medical profession.

—MSMW

CASE REPORTS

Refer to: Baum RS, Welch TG, Bryson AL: Spontaneous pneumopericardium. West J Med 125:154-156, Aug 1976

Spontaneous Pneumopericardium

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PNEUMOPERICARDIUM is a rare condition usually associated with trauma, infection, fistula formation or iatrogenic disease states.[1-10] Spontaneous or idiopathic pneumopericardium is even more unusual and has been ascribed to rupture of a pulmonary alveolus with perivascular dissection back into the pericardium.[11-13] This report describes a 14-year-old boy with pneumopericardium following an episode of weight lifting. Clinical and radiologic features in spontaneous pneumopericardium are characteristic and the course is benign if the entity is looked for and recognized.

Report of a Case

A 14-year-old white boy entered David Grant United States Air Force Medical Center with a one-day history of dull substernal chest pain which worsened with deep breathing. He had been well until the day before admission and there was no history of fever, rash, joint pain or gastrointestinal discomfort. Two days before admission the patient had been lifting weights as part of a regular exercise program. Past history was unremarkable. There was no known exposure to tuberculosis.

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Opinions expressed are those of the authors and do not represent official Air Force Policy.

Submitted September 24, 1975.

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On physical examination, the patient was found to be alert, cooperative and in no acute distress. Blood pressure was 110/68 mm of mercury, pulse was 80 beats per minute, and respirations 20 per minute. No abnormalities of the head, ears, eyes, nose, throat or mouth were noted. A pectus carinatum deformity was seen on examination of the chest. The lungs were clear. There was a coarse systolic sound audible along the left sternal border. Heart sounds were normal and no murmurs were heard.

A roentgenogram of the chest showed the presence of pneumopericardium without any active pulmonary infiltrates or presence of pneumothorax (Figure 1). Electrocardiographic findings were within normal limits. The remainder of the laboratory workup gave results within normal limits, including a negative tuberculosis tine test, a negative cineesophagram and normal findings on a cardiac series with a barium filled esophagus.

The patient remained afebrile throughout the time in hospital. The chest pain resolved over the first 48 hours with conservative therapy. A repeat x-ray study of the chest showed no increase in the pneumopericardium. Findings on a follow-up roentgenogram one month later were normal and the patient was asymptomatic.

The patient had an additional episode of chest pain about a year later, again following an episode of weight lifting. There was no friction rub, electrocardiographic findings were normal and a roentgenogram of the chest again showed the presence of pneumopericardium. The pain resolved in two days with no therapy and a roentgenogram of the chest showed no abnormalities.

Discussion

Pneumopericardium was first described in 1844 by Bricheteau.[1] Since then, numerous cases have been reported and several common causes have been postulated. These include (1) trauma—secondary to perforation of the pericardium by a foreign body,[1-4] (2) infectious—secondary to gas-producing bacilli in the pericardial fluid,[1-4] (3) fistula formation—secondary to perforation of a neighboring viscus such as esophagus, stomach, liver abscess or bronchus[5,6] and (4) iatrogenic—secondary to pericardiectomy,[8] assisted

positive pressure ventilation in neonates,[8] esophagostomy[9] and pneumoencephalography.[10]

Although these causative factors were investigated in the case described here, no specific cause was identified. Nevertheless, the mechanism by which pneumopericardium developed in this case probably conformed to the observations of Macklin[11] in which alveolar rupture under sudden expiratory pressure (Valsalva) leads to dissection of air through the interstitial tissues of the lung and is guided along the sheath of the pulmonary vascular system, the mediastinum and then into the pericardial sac itself. Our patient had been weight lifting two days before clinical presentation and this could account for an alveolar rupture and subsequent dissection into the pericardium. Similarly, two cases of pneumopericardium in the immediate postpartum period have been attributed to Valsalva maneuver during labor leading to alveolar rupture,[12] and therefore conforming to Macklin's observations. In addition, this mechanism has also been reported to occur in acute asthma.[13]

Mauer and co-workers found in dogs that the increased intrapericardial pressure occurring with pneumopericardium may restrict ventricular filling. In our case there was no clinically evident hemodynamic embarrassment, probably due to the small amount of air present.

Symptoms of pneumopericardium may be absent or may include dyspnea, precordial chest pain, upper abdominal pain or syncope. Physical findings may be absent or may include associated subcutaneous emphysema, precordial hyperresonance, and a bubbling, crackling or crunching sound synchronous with the heart beat or a friction rub best heard in the left lateral decubitous position.

The feature, shown on x-ray studies, of a radiolucent space around the heart shadow surrounded by and defining a thin pericardial membrane, as seen in our patient, is characteristic and diag-

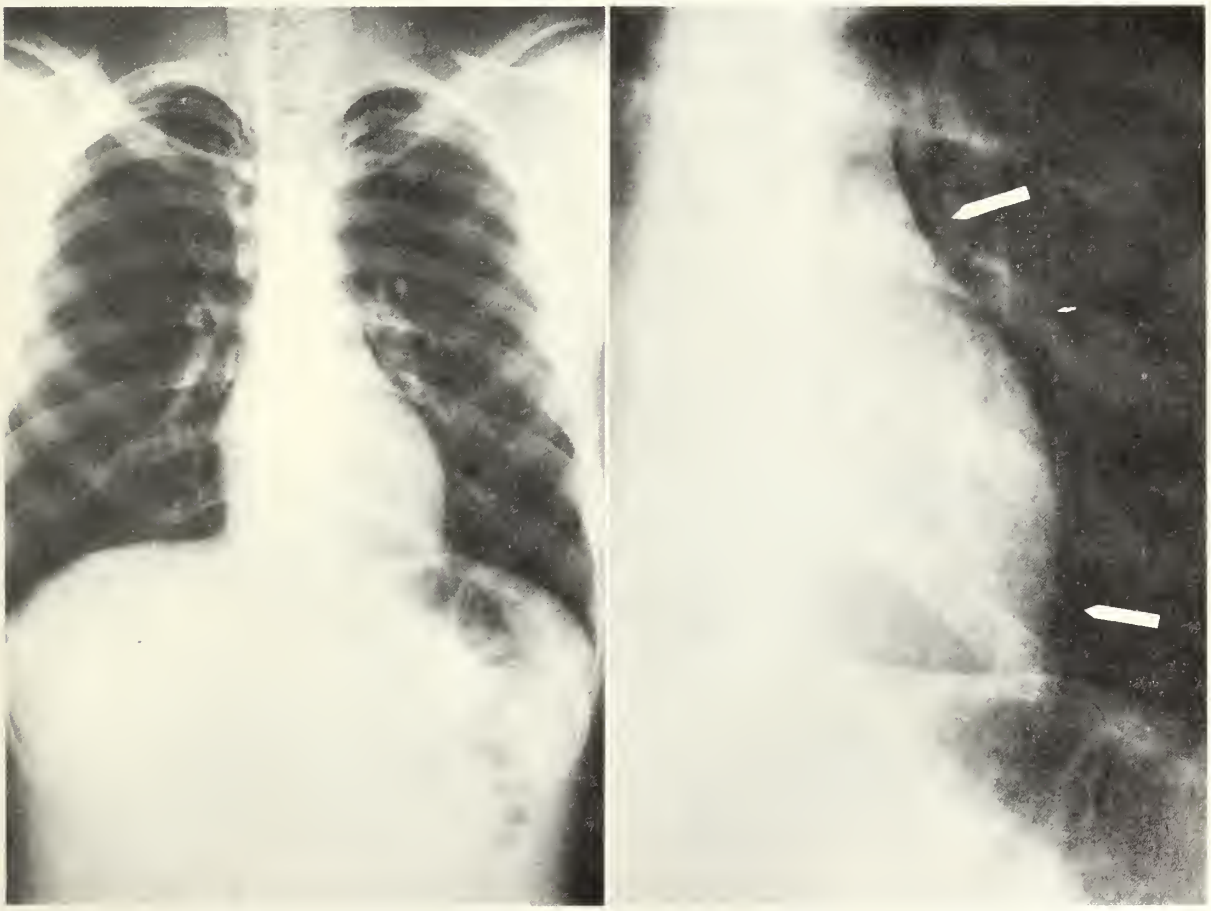

Figure 1.—Left, posteroanterior roentgenogram of the chest showing a radiolucent space along the left heart border surrounded by and defining a thin pericardial membrane. **Right,** enlargement showing the pericardial membrane (arrows).

nostic. The electrocardiogram is characteristically normal, and signs of pericardial injury are conspicuous by their absence, unless there is an infectious cause as in pyopneumopericardium.

The recognition of pneumopericardium in the presence of a history consistent with pericarditis, but with a normal electrocardiogram and characteristic findings on a roentgenogram of the chest, is important since the management and prognosis is dependent upon the underlying disease state as mentioned above. In the absence of any obvious underlying cause, a history of recent exertion, especially that involving a Valsalva maneuver, should be sought. Mistaking this presentation for pericarditis would lead to an error in therapy, since such cases of spontaneous or idiopathic pneumopericardium are usually associated with small amounts of air and have an excellent prognosis with conservative management.

Summary

Pneumopericardium is an uncommon entity with numerous possible causes. Clinically it often presents with pericarditis. Its spontaneous occurrence following prolonged Valsalva maneuvers is associated with a benign clinical course. In otherwise healthy patients presenting with pericarditis, proper recognition of this condition and its classic radiologic findings may prevent unnecessary therapy.

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Refer to: Freedman SR: Histiocytic medullary reticulosis with central nervous system involvement. West J Med 125: 156-159, Aug 1976

Histiocytic Medullary Reticulosis with Central Nervous System Involvement

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HISTIOCYTIC MEDULLARY RETICULOSIS (HMR) is a malignant disorder of proliferating histiocytes characterized by a rapidly progressive and fatal course of fever, wasting, generalized lymphadenopathy, hepatosplenomegaly and pancytopenia. It was first described in 1939 by Scott and Robb-Smith,[1] who distinguished it from other malignant lymphoreticular diseases by characteristic morphologic features in lymph node and spleen. This entity has been further characterized immunologically as a malignant proliferation of the M-cell lineage (monocyte-macrophage-histiocyte).[2]

Central nervous system involvement in HMR is rare,[3] reported only in isolated cases.[4] The following case report describes a patient with HMR in whom antemortem manifestations of neurologic dysfunction and extensive pathologic involvement of the central nervous system were present.

Report of a Case

A 44-year-old woman was admitted to hospital at Santa Clara Valley Medical Center in October of 1972 for the evaluation of progressive lethargy, anorexia, abdominal discomfort, chills and fever, and weight loss occurring insidiously over four months. Four weeks before admission, episodic temporal headaches developed, followed by lightheadedness. On initial physical examination, the patient appeared ill, with moderate hepatosplenomegaly, mild ascites and wasted extremities.

Laboratory studies gave the following values: hematocrit reading, 36 percent; hemoglobin, 11.1 grams per 100 ml; leukocyte count, 3,800 per cu mm, with 51 percent neutrophils, 4 percent band

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forms, 28 percent lymphocytes (a few atypical) and 12 percent monocytes. The red cells were hypochromic with pronounced microcytosis, and the reticulocytes were 4.5 percent. Serum iron concentration was 117 μg per 100 ml (normal: 65 to 145); binding capacity, 212 μg per 100 ml (normal: 260 to 425). Results of bone marrow biopsy and aspirate studies showed erythroid hyperplasia. The platelets were 235,000 per cu mm; the prothrombin time was 70 percent. Alkaline phosphatase value was 5.1 Bodansky units (normal: 1 to 4.5); lactic dehydrogenase, 1,260 Burger-Broida units (normal: 100 to 350), and total bilirubin, 0.9 mg per 100 ml (normal 0.2 to 1.2). On serum protein electrophoresis, total protein was 5.1 grams per 100 ml (normal: 6.2 to 8.5); albumin, 2.2 grams per 100 ml (normal: 3.5 to 4.5) and the pattern unremarkable. Immunoelectrophoresis showed decreased gamma G and gamma M fractions. Cultures and serologic tests for bacteria, fungi and viruses were negative.

In November 1972 hepatosplenomegaly and grossly normal lymph nodes were noted on laparotomy. The spleen was found to weigh 600 grams with congestion and histiocytic infiltration of the red pulp. No significant abnormality of the liver was seen. Atypical histiocytic proliferation with a sinusoidal pattern was noted in a paraaortic lymph node. Findings on studies of bone marrow showed erythroid hyperplasia. The diagnostic impression at discharge was occult malignancy.

During the next 3½ months, fever, lethargy, anorexia and weight loss persisted. Bilateral leg pain became more severe. Findings on a gastrocnemius muscle biopsy study showed myopathy with necrotic muscle fibers. On readmission of the patient for intense lower extremity pain (March 1973), examination showed persistent, moderate hepatomegaly and pronounced pitting edema, distal hypalgesia and hyporeflexia in the lower extremities. During the stay in hospital, episodic confusion, agitation and inappropriate responses to questioning, with an inability to name objects, were noted. On brain scan, an area of faint uptake in the left frontoparietal region was seen and this was substantiated on two subsequent studies. Cerebral angiography gave normal findings. An electroencephalogram showed diffuse cerebral dysfunction of a nonspecific type. On three occasions results of studies of cerebrospinal fluid showed protein levels in the range 110 to 150 mg per 100 ml (normal: 10 to 45); glucose, 55 mg per 100 ml (normal: 40 to 70); 1 to 5 leukocytes per cu mm and no malignant cells. Therapy with prednisone, 60 mg per day, was begun on May 13. Findings on lymphangiography suggested an enlarged paraaortic lymph node, and a biopsy study during laparotomy, June 1973, showed infiltration of the subcapsular sinuses by undifferentiated malignant cells, retrospectively interpreted as histiocytic medullary reticulosis. A sinusoidal and periportal infiltrate of atypical histiocytes was observed in the liver. Cyclophosphamide, 100 mg per day, was added to the treatment regimen on June 14 and was well tolerated without evidence of toxicity.

Mentation continued to deteriorate. The final admission, August 1973, was prompted by a symmetrical tonic-clonic seizure episode with deviation of the head and eyes to the left and postictal obtundation. Findings on neurologic exami-

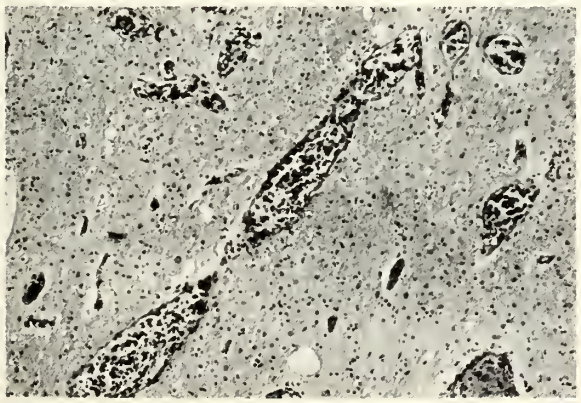

Figure 1.—Malignant histiocytes confined within the lumina of vessels of the subcortical white matter in the hippocampal gyrus. (Hematoxylin-eosin, reduced from original magnification 100×).

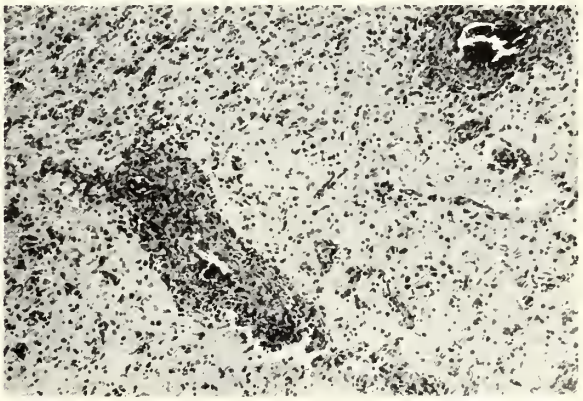

Figure 2.—Perivascular spaces with malignant histiocytes and infiltration of surrounding thalamic neuropil (Hematoxylin-eosin, reduced from original magnification 100×).

nation showed anisocoria with right fixed pupillary dilatation. Lumbar puncture yielded clear cerebrospinal fluid with a protein content of 190 mg per 100 ml, and nonmalignant cells. No abnormalities were shown on brain scan. Progressive unresponsiveness ensued, and the patient died on August 21, 1973 after 14 months of illness.

Necropsy

At necropsy, malignant histiocytes were found to be present in lymph nodes, kidney, bladder, heart, lungs and bone marrow. The proliferating malignant histiocytes were large, pleomorphic and atypical. The nuclei were large with variably fine to coarsely-clumped chromatin, prominent nucleoli and an irregular membrane. Cell borders were indistinct, and the cytoplasm was abundant, pale, blue-gray to pink and vacuolated. Erythrophagocytosis was observed in scattered cells.

Peripancreatic and paraaortic lymph nodes were small, firm, yellow-tan in color and 4 to 6 mm in average diameter. Aggregates of malignant histiocytes occupied the subcapsular and medullary sinuses without effacement of the nodal architecture.

The right and left kidneys weighed 250 and 320 grams, respectively, and were unremarkable on gross examination. Viewed microscopically, capillaries of scattered glomerular tufts and peritubular networks were engorged with malignant histiocytes. Similar intravascular aggregates were found in the bladder, heart and lungs. The bone marrow was focally infiltrated with malignant histiocytes.

Study of the 2,600 gram liver showed atypical histiocytes in the sinusoids. The skin, gastrointestinal tract and pancreas were found to contain intravascular collections of atypical histiocytes.

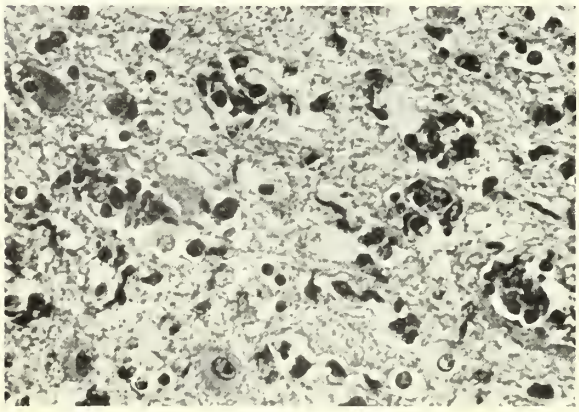

Figure 3.—Infiltrate of malignant histiocytes, pleomorphic microglia and reactive astrocytes in thalamic parenchyma (Hematoxylin-eosin, reduced from original magnification 400×).

Neuropathology

The fresh brain weighed 1,100 grams. The external configuration of the brain was unremarkable. Coronal sectioning after 10 percent formalin fixation disclosed multiple, scattered areas of cortical thinning with focal linear necrosis most prominent in the parietooccipital region. A circumscribed area of blue plexiform discoloration, 0.5 cm in diameter, was located in the subcortical white matter of the right frontal pole. The basal ganglia, cerebellum and brainstem were unremarkable on gross examination.

On microscopic examination, neoplastic infiltration was extensive. Dense clusters of malignant histiocytic cells, with morphologic features similar to those described in other organs, occupied the lumina of medium and small vessels (Figure 1). These cells in many instances infiltrated the vessel walls, distending the perivascular space, and in some areas diffusely infiltrated the surrounding brain (Figure 2). In many small vessels, the cells were present only in the perivascular spaces. In the parenchyma, many cells assumed a more elongated, flattened, twisted, bizarre appearance and intermingled with cells identifiable as pleomorphic microglia. Mitoses were moderately frequent and erythrophagocytosis was occasionally present. Reactive astrocytosis was present at the periphery of areas of involvement (Figure 3). In some regions of the frontal cortex cellular infiltration involved the subpial regions and overlying subarachnoid space. Elsewhere, tumor cells were confined within the lumina of leptomeningeal vessels. Reticulin stains showed increased concentric, perivascular, reticulin fibers investing small groups of tumor cells. Tumor involvement was extensive in the frontal cortex, thalamus and internal capsule and more focal in the putamen, globus pallidus, hypothalamus and temporal lobe. The discolored area in the right frontal white matter showed telangiectasia with thin-walled, endothelial lined spaces distended with malignant histiocytes. Diffuse vascular, perivascular and parenchymatous involvement was present in the midbrain tectum, periaqueductal gray matter, substantia nigra and cerebral peduncles. The floor of the fourth ventricle in the upper pons was also involved while in the basis pontis and medulla, malignant cellular aggregates were confined within

blood vessels. In the cerebellum, there was local infiltration of white matter and dentate nucleus.

The grossly visible cerebral cortical lesions represented pseudolaminar necrosis characteristic of an anoxic episode occurring several weeks before death. Focal areas of patchy Purkinje cell loss and proliferation of Bergmann's glia characterized the anoxic process in the cerebellum. (The case was reviewed by Drs. Lucien J. Rubinstein and Roger Warnke, Department of Pathology, Stanford University, who substantiated the diagnosis.)

Discussion

Histiocytic medullary reticulosis is a systemic proliferation of malignant histiocytes occurring predominantly in the lymph nodes, spleen and bone marrow. In lymph nodes the proliferating cells permeate the subcapsular and medullary sinuses, generally preserving or only partially distorting the nodal architecture. In the spleen the proliferation tends to occur in the red pulp sinuses, with partial obliteration of the white pulp. Hepatic involvement is sinusoidal and periportal. The neoplastic histiocytes have variable nuclear pleomorphism, prominent nucleoli and abundant pale cytoplasm with phagocytic material including erythrocytes. The clinical course is relentless and ultimately fatal, and the response to treatment disappointing.[5,6]

The pattern of lymph node involvement in this case is characteristic of histiocytic medullary reticulosis. Although the histiocytic infiltrate in the splenic red pulp is atypical and not cytologically malignant, a diagnosis of histiocytic medullary reticulosis is still tenable since cases have been observed without cytologically malignant histiocytes in the spleen. The deceptively bland appearance of the histiocytic infiltrates not only makes the distinction from a reactive process difficult,[7,8] but also accounts for the frequent inability to diagnose the disease antemortem.[5]

The unusual feature here is the extensive infiltration of the central nervous system. Other lymphoreticular neoplasms can involve the brain either primarily (reticulum cell sarcoma-microglioma) or as a manifestation of systemic disease.[9-11] In the latter instance, dural and leptomeningeal infiltration occur most commonly, although brain parenchyma occasionally can be involved,[10,12,13] producing a morphologic pattern similar to this case of histiocytic medullary reticulosis.

In contrast to the scarcity of documentation of central nervous system involvement in histiocytic medullary reticulosis is the relatively frequent occurrence of brain involvement in an uncommon, familial, lymphoreticular disorder of infancy and early childhood, designated "familial hemophagocytic reticulosis."[3,14-16] The clinical characteristics, except for age and familial occurrence, are similar to histiocytic medullary reticulosis, and histiologic features are identical.[17,18] The relationship of these separately described disease entities, as well as other disorders of proliferating histiocytes, remains to be elucidated by evolving concepts of pathogenesis and nosology.[19,20]

Summary

In a 44-year-old woman persistent fever, weight loss, hepatosplenomegaly, and neurologic symptoms and signs developed. The characteristic morphology of histiocytic medullary reticulosis in lymph nodes was shown at autopsy. Involvement by malignant histiocytes occurred in many organs, including the brain, where parenchymal infiltration was extensive. The clinical, general pathological and neuropathological features of this unusual occurrence are presented, and the relationship to familial hemophagocytic reticulosis is discussed.

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Medicine and the Quality of Life

QUALITY OF LIFE increasingly is being identified as a goal of medicine and health care. In the July issue, the editors began a forum for discussing the actual and ideal relationships between medicine and the quality of life by printing seven articles expressing differing views. The following comments were generated by those articles.

Readers are invited to take part in a continuation of this forum by submitting their comments, written as succinctly as possible. As many of these as space permits will be published in future issues. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement to summarize the dialogue that has taken place.

Dual Responsibilities

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THE PURPOSES to which we live are a part of the social-political system into which we are born. If our system is one that encourages self-interest, accumulation of private goods and development of the spirit as a personal responsibility, then our purposes will be considered positive and our quality of life good to the extent that we achieve these objectives. If our system is one that submerges self-interest to community interest, personal enterprise to group enterprise and personal spiritual growth to the development of community standards, then the goodness or positivity of our quality of life will be measured by the extent to which we achieve these community goals.

The definition of a positive quality of life as distinct from absence of disease will never be considered a responsibility of the professional role of those few citizens who elect to aid the sick and suffering. Society at large will determine the purposes and hence quality of life and will adapt its medical care systems to fit these purposes. Our present problems arise not from a new concern for something called quality of life but rather from a growing minority who feel that a different quality of life is needed. This new concern with ultimate purposes of less personal collection of worldly goods, less consumption of worldly resources and greater group activities will, if successful, define a new quality of life in the years ahead.

The professional activity of medical workers remains the immediate care of the individual patients. This is a limited role but one requiring devotion, skill and a continuing close one-to-one relationship. I feel that the ability to care for the sick is a demanding, exhausting task that merits more rather than a diluted attention. The great hazard is not that the medical care system will fail to define quality of life—it never can—but rather that the struggle for such definition will impair the care of the sick.

Such thoughts as expressed above are not new or original. They are part of the substance of many of the statements in the July forum. Writing now as a physician, the problem seems to be how does one separate the professional role of a medical worker from the role as a citizen—as a person? On the one hand, it seems arrogant and naive to assume that medical workers should do more professionally than aid the sick and suffering. On the other hand, medical workers have a unique opportunity to see the devastating effects of disease on a person's life and life-style. This knowledge must and should be transmitted professionally and socially through the channels we use as medical workers and those we use as citizens.

A medical worker faces the difficult task of protecting the integrity and credibility of his particular role with the sick and also developing his general role as a contributing citizen. This process should start early in our education and I would make a plea for an educational process that recognizes the role that liberal arts and humanities play in our quality-of-life decisions. This recognition should result in a continuing education pattern that utilizes the publications and expressions of the community at large. At the same time that this part of one's existence is enriched, there should be no neglect of the strictly medically oriented education that goes on throughout a professional career. I see the role of medical organizations as a continual effort to upgrade the professional skills of their members and, by example and precept, to keep their members aware of a wider world in which we all participate to make the decisions that will ultimately result in "quality of life."

In summary, I believe the medical care system has a restricted role in defining quality of life, that this restricted role is a worthy one and one requiring a great deal of effort, compassion and skill. Those professional workers whose lives have been largely dedicated to the care of the sick and the suffering owe those patients the best of themselves that they can give. An entirely different role is the role played by the medical worker when he joins the general gathering of citizens in defining quality of life. This latter role needs emphasis in all levels of education.

Refer to: Petit DW: Dual responsibilities, *In* Medicine and the quality of life—A forum. West J Med 125:160, Aug 1976

The Status of Women

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ANY DISCUSSION of the quality of life must consider the changes that have been occurring in the lives of women as a class, the contributions of medicine to these changes and their effects upon the health of patients, both men

and women. A related point is the emergence of an additional work force and, as a result, the desire for further modifications which could improve the quality of life for all.

Until recent times, the birth of large numbers of children was indispensable for the economic viability and survival of a family. Since the capacity to conceive and give birth is unique to women, bearing and rearing children occupied the position of greatest importance in their lives. They met their responsibilities and fulfilled their obligations willingly, actually pleasurably. With the population explosion, and the need to curtail further growth, unlimited child bearing ceased to be the service to humanity so essential to perpetuation of the human race it had been in the past. This in no small measure was due to medical advances that resulted in diminished infant mortality, effective immunization against childhood diseases, new definitive treatments and prenatal detection of developmental defects. The availability of efficient and facile contraceptive devices and abortion gave women more command over previously uncontrollable events in their lives and this increased their options.

Great technological advances now permit machines to do the heavy work formerly done by men, and free women from many time- and energy-consuming household tasks which at one time provided great satisfaction, gratification and opportunity for creativity. The pleasures and exhilarations they derived from the old way of life were lost and the loss necessitated a search for substitute compensations as well as outlets for the time and energy now available to them. Additional education, increased knowledge and awareness provided by improved communication delighted and enlightened them and resulted in recognition of their potential by themselves and the rest of the world. The ubiquitous discriminatory practices, which denied women the privilege of participating in many endeavors, and relegated them totally to the home and the tasks of child bearing and rearing heretofore indispensable to mankind's survival and well being, no longer served their previously useful purpose. Their eradication could allow full use of women's special endowments. Women's greater longevity, lower suicide rate and lower incidence of senile dementia when compared with men's represent additional desirable attributes in a new source of providers.

The emergence of women from the home, their capability and desire to share in outside work and contribute toward the financial support of the families with their earnings, could relieve men of some of the financial responsibility that falls heavily upon them in this competitive world and which, all too often, deprives them of the pleasure of close contact with the children they strive so hard to support and to whose development they would like to contribute to a greater extent. More equable distribution between the sexes of the demands of the economic world in business and professions might lessen the stresses and strains and, as a consequence, tend to equalize the life span, and favorably influence the suicide rate and incidence of senile dementia.

There no doubt will continue to be mature, emotionally and physically healthy women who derive their greatest gratification and most meaningful satisfactions, and who also make invaluable contributions, in functioning as mothers, wives and homemakers. This preference merits respect and is not to be demeaned. They must not be intimidated by demands for compliance with the trend toward work outside the home that some groups of women may make. Such uniformity might well eventuate in mediocrity and destroy the very freedom of option indispensable to the improved quality of life to which we all aspire. Not to be overlooked, however, is the existence of a substantial body of women whose preferences and capacities permit fully adequate functioning in a dual role in the domain of the home and business or professions. Both men and women should enjoy an equally wide range of opportunities from which to select those best suited to their particular needs, wishes, personalities, inclinations, talents and potentials with resultant optimal development, gratification and contribution.

In his classical study entitled "Das Mutterrecht," Johan Jacob Bachofen, a philosopher of history who was more concerned with the inner life of human beings than the external characteristics of human development wrote: "Raising her young, the woman learns earlier than the man to extend her loving care beyond the limits of the ego to another creature, and to direct whatever gift of invention she possesses to the preservation and improvement of another's existence." Studies of animals abound with illustrations of precisely these proclivities in the females of many species.

How helpful the hormonally determined psychological characteristics which derive from that uniquely intimate bond between mother and child could be in patient care, and how great is the need for such traits if we are to improve the quality of life by balancing with humanization the automation, computerization and depersonalization with which technological advances have both endowed and afflicted us. The present trend of allotting more places in medical schools to women, if complemented by their occupancy of a greater number of important positions on faculties, could well be a step in the direction of fulfilling that need. Medicine would doubtless benefit were it to take advantage of the increased and qualitatively different work force that might thereby serve not only as an external outlet for women's available energy, but also as inner experience to compensate for forgoing that measure of pleasure afforded by child bearing and child rearing. There exist in women strong yearnings for inner experiences which they have satisfied, among other ways, by interest in art, music, literature and history. Men might well lengthen their lives and curtail some of the stresses and strains to which they subject themselves were they to do likewise instead of viewing such interests as fruitless, impractical or feminine, and accordingly, suppressing or denying them.

In some areas where women have adopted men's behavior the results have been disastrous. Drinking like men has increased alcoholism, and smoking like men, lung cancer. Women need to develop sufficient and appropriate confidence in their feminine attributes to feel free to bring them unapologetically to all their endeavors and men conversely should not feel a continuous compulsion to assert what they regard as the indispensable attributes of masculinity. Too often the latter inclination results in the quest of power and its injudicious, unethical even destructive use, particularly when the advances, technological and scientific, including the medical, become instruments of such power. Women's values and interests have never been adequately reflected in our way of life. It is possible that given the chance, they could help the world out of its present chaotic state by tempering the aggression, which if permitted to go unbridled might well culminate in total annihilation. Mature development includes transcending gender, with true empathy and regard for both sexes and what each has to offer. Both halves of humanity must be embraced and reconciled in all forms of work.

An improved quality of life should result from an increase in the number of women who participate as equally paid responsible members of the work force and who hold important demanding positions in professions, educational institutions, governmental agencies and decision making. With the increased labor contingent they provide and the earnings they contribute to the family funds, and with continued technological progress constructively employed, there will be shorter work weeks for all. Correspondingly the responsibilities of home and family may be more happily divided between husband and wife, and increased leisure enjoyed by both and their small family. Should such be the case one would be justified in predicting a reduction of morbidity and mortality due to certain stress induced illnesses as peptic ulcer, dermatitis, hypertension and coronary artery dis-

ease among others.

Although it is beyond the scope of medicine to bring about all these modifications, physicians must recognize and acknowledge that dissatisfied, overenergized women without rewarding outlets are candidates for development of emotional, mental and physical illnesses; that the men with whom they share their lives will feel the impact of these reactions and respond to them bodily or emotionally to their own detriment; that the pressures to which serious and ambitious men subject themselves can be lightened, and that the illnesses following in the wake of such stressful lives can be diminished by a reciprocal division between men and women of the obligations and responsibilities of a shared relationship. There exists presently a disequilibrium that requires correction. Any assistance on the part of the medical profession to restore the balance between the sexes can be regarded as a form of preventive medicine, and thus a contribution by physicians toward the improvement of the quality of life.

Refer to: Tausend H: The status of women, *In* Medicine and the quality of life—A forum. West J Med 125:160-162, Aug 1976

Biological Advances

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My interests move, perhaps predictably, to the more serious and less temporal aspects of the seven statements on quality of life in the July issue:

- The outlook for the future of science and quality of life beyond the step-by-step increased understanding of disease and
- The contributions and limitations of health related to quality of life.

That is not to say that such questions as an efficient system, reduction of the risks of modern medicine, ethical principles, basic rights, over-promise and a relook at basic human needs are not important, indeed urgent, needs of our society.

Rather, I am puzzled about the impact of much more extension of life expectancy or freedom of disease on our aggregate sense of increased quality. For individual people the situation is quite different. Health, especially in later years, often almost entirely determines the quality of life for the individual person. Yet in a nation where the chances of long life and the prospect of increasing freedom from disease on the basis of current knowledge exists, the points raised in the articles by Cooper and by Dubos are most relevant.

Even more intriguing is the current question of the state of the art in the biological sciences. The conceptual implications of the DNA recombinate story may exceed any previous development in human history. Such giant strides in understanding (should this turn out to be the biggest of all) inevitably affect all aspects of subsequent life, including its quality.

Refer to: Marston RQ: Biological advances, *In* Medicine and the quality of life—A forum. West J Med 125:162, Aug 1976

Factors Outside the Province of Medicine

NORMAN Q. BRILL, MD, Los Angeles
Professor, Department of Psychiatry, University of California, Los Angeles, School of Medicine

As has been pointed out in the July issue, there is indeed an important role that medicine has played, and can and will continue to play, in improving the quality of life of all people. Medicine can well be proud of the degree to which dreaded infections of childhood and adulthood have been controlled or eliminated and of the removal of the awesome fear of childbirth that was prevalent in the early days of this country. Tuberculosis and syphilis are no longer the dreaded diseases they once were. Impressive improvements have been achieved in anesthesia, surgical techniques, postoperative care, and the treatment of the mentally ill. Outstanding advances have been made in achieving accurate diagnosis of disease through the use of sophisticated clinical, laboratory and radiological techniques. Training of paramedicals has extended and improved emergency medical care.

Along with the improvement in physical health of the population of the United States there is a diminished fear of illness and a greater sense of freedom from the threat of disease and disability. As a consequence there is a vastly improved quality of life. It is only reasonable to expect, if one can judge from the past, that there will be additional advances in the next century in prevention, and in treatment of illness that will contribute even more to the quality of life.

However, society will continue to pay a price for all advances as it has done in the past. The increased life expectancy has led to the need to support an enlarging senior population, with emotional and financial burdens for the rest of society and nursing homes for the elderly that so often detract from the quality of life to which they are supposed to contribute. Advances in medicine have contributed to the development of unrealistic expectations of doctors and to the malpractice mess now facing the public and the medical profession. People expect that there is a cure for every disease and a remedy for every symptom. In attempting to cater to these expectations, physicians may have unwittingly helped create a drug dependent society.

Unrealistic expectations from medicine have been accompanied by unrealistic expectations in other areas of life. There are humanistic but misinformed persons who insist that if poverty, racial prejudice and male chauvinism are eliminated there will be no mental illness. They seem to forget that poverty and prejudice are neither necessary for nor sufficient to produce mental illness. There are, for example, plenty of affluent citizens who suffer from the same disorders that the less fortunate do.

It seems that emphasis has shifted from helping individual persons adjust to society to having society adjust to its individual members, and it seems that social reform has to be justified on the basis of health reasons rather than for ethical, humanitarian or political reasons.

Poverty or prejudice now must be eliminated, not for ethical or humanitarian reasons but because they are bad for mental health. In order to permit women to take time off with pay during pregnancy, pregnancy had to be regarded as a disability putting it in the category of illness rather than a natural biologic event.

Another example of society adjusting to individual persons rather than expecting them to adjust to society is the recent ruling that instruction in elementary schools will have to be given in whatever language the pupils know—Spanish, Chinese or Arabic as the case may be. While the reasons for this are obvious it is a far cry from the expectation years ago, when there were mass

migrations of Irish, Germans, Scandinavians, Italians and Jews to this country, that people coming to this country had the responsibility to learn the language of the country.

It is agreed that health is a crucial factor in determining the quality of life; however, it would be a mistake to forget that there are many other factors outside the province of medicine that play very important roles. The improved quality of life that has resulted from the impressive advances in medical care and standards of living, seems to have been accompanied (no causal relationship is implied) by a diminishing morality, disturbed interpersonal relationships, more anxiety about employment and security, greatly increased divorce and crime rates, and increased human unhappiness and world tension.

There are some who look to physicians to solve all of these problems of living and of society, and to ameliorate all unhappiness, anxiety, conflict, discomfort, unfairness, inequity and prejudice. This is not what physicians had been trained to do nor do they have any special competence in these fields. Physicians should recognize and define those things in society that have a deleterious effect on health, urging those members of society whose job it is to do so to ameliorate them. Physicians, for instance, can discover that typhoid fever results from exposure to a contaminated water supply. They should treat the patient, but leave it to sanitary engineers to correct the basic problem.

People increasingly show a tendency to blame someone else for everything that happens to them. Any untoward experience or deprivation or disappointment is regarded as the fault or failure of society. At a White House briefing on crime, one social agency representative implied that society had somehow failed a person who has committed a crime and that therefore no one should be imprisoned for a crime.[1]

As society has tended to give a higher priority to the rights and needs of individual persons and a lower priority to the rights and needs of society, the quality of life has deteriorated. More and more people are afraid of being mugged, robbed or killed in the streets or at home. People are afraid to go out of their homes at night and hotel doormen in some cities warn the hotel guests about walking on the streets around the hotel.

Margaret Mead in her address to the American Psychiatric Association in May 1975, criticized psychiatrists who, although they know a great deal about broken homes and their effects on children, have done little to protect children from emotional damage and child abuse. She said society is in an exceedingly dangerous period. People do not understand why muggings and arson are occurring in such great volume or why the public has such enormous anxiety over economic matters. "How we bring up children isn't strong enough to withstand such anxieties, change and ambiguity." "The profession may be placing too much emphasis on a social consciousness . . . it might better attempt to bring out the best in people, like that brought out in time of war: their sacrifice, loyalty, and unselfishness."[2]

REFERENCES

1. The Retired Officer, page 10, Aug 1975. The Retired Officers Association, Washington, DC

2. Mead M: Address to American Psychiatric Association, May 1975. Clin Psych News 3:9, 1975

Refer to: Brill NQ: Factors outside the province of medicine, *In* Medicine and the quality of life—A forum. West J Med 125:162-163, Aug 1976

Human Nature and the Quality of Life

PETER M. LEWIS, MD, Riverside, CA

Head, GI Clinic, Riverside General Hospital; Assistant Clinical Professor, Department of Medicine, Loma Linda University School of Medicine, Loma Linda, CA

THE SEVEN STATEMENTS by health leaders and administrators in the July issue all touch on pertinent points but in no case, I think, is there a perception of certain fundamental human attitudes essential to any discussion of how medicine may relate to the quality of life. Quite rightly, Mr. Sobel indicates that more than technology is needed to effect some kind of lasting health. Dr. Cooper indicates that medicine might involve itself in prevention of conditions that lead to illnesses, medical and social. Dr. Dubos, on the other hand, decides that medicine may not be equipped to do much, really, and that the technical improvement of health may impart "joie de vivre" that will allow a person then to exploit his potentials. I agree with Dr. Fuchs that one neglected attitude of medicine would be to teach people to be well and to reduce dependency on medical care, physicians and institutions. He implies that success in medical care should reduce the need for medical care.

Dr. Jonsen uses the word "purposefulness" as the prime function of human beings and indicates that medicine, through its social and technical equipment, might improve this ability for purposefulness. However, he touches on the sore point that humans are good and bad—"ambiguous," and that this produces a tangle of problems that may interfere with the "ability of humans to formulate and implement purposes." Dr. Moser correctly points out that physician responsibility and patient freedom are both at work and that to make proper decisions a partnership between patient and physician is needed. Finally, Dr. Elam discusses unfulfilled expectations and erroneous goals, and supposes that physicians will assume the role of "transformers of life as a whole" and medicine will become a vital part of a higher quality of life. He does not say how this is to be accomplished.

In my mind, all of these have skirted the issue; some have touched on points of importance and interest, but none has quite struck the mark. It seems that several thousand years of recorded human history might have taught us something about the facts of human nature and how human beings actually do respond, and to what they respond positively and constructively. If, as Solzhenitsyn asserts, the "aim of life for each of us is not to take a boundless pleasure in material goods, but to take our departure from the world as better persons than we arrived at it, better than our inherited instincts would have made us," then it follows that "the sum of such progressions that can be called the spiritual progress of humanity" is a goal that may have something to do with the quality of life.

Not that all of us *want* to either improve ourselves or to contribute to a community or world ethic. This attitude is incomprehensible or unappealing to many. Nevertheless, if the quality of life is to be improved and truly achieved, then some axioms derived from a sense of history about human nature need to be observed.

I would say that for the quality of life to be improved for any individual person, human nature must be understood and the elements entering into that quality must be in tune with human nature. If one assumes that premise, then a view of human history takes over, and the studies of social psychologists—as diverse as Konrad Lorenz and Desmond Morris—may be examined. Those things that will work for human beings and will bring them happiness must be analyzed and put

down. It follows that things that may be appealing superficially, if out of step with human nature, simply will not long work. Thus, food in the belly alone, or a plethora of material goods, being at opposite ends of the spectrum, will not in themselves improve the quality of life.

What is needed instead is to define the axioms taught by history, and then to use them as guides to improve the quality of life. Some words and phrases spring to mind, such as work, respect, personal responsibility for one's destiny, community responsibility for each other, belonging, humor. Other words associated with those include opportunity to exploit one's ingenuity, fear and its prevention or assuagement, a "place" or sense of belonging, confidence and self-love.

These are word symbols and there is not space to develop and integrate each of them into the programs to which I allude. Nevertheless, medicine—both organized and personal—has a place here. Physicians, particularly those dealing directly with people, are in a position to make some judgments about human nature. Physicians need to be educated in human nature and about how human beings work. There needs to be more education in medical school, and after it, about the relationship between human nature and disease states. Then physicians should by personal example try to portray the elements that contribute to personal fulfillment. If these elements are axiomatic, then they pertain equally to all humans, whether or not they are immediately appealing to them. Work, whether one feels like doing it or not, is probably necessary to a healthy mind. Rewards, material and psychological, without work are pith and of no lasting value. Joy in each day and each hour is a quality that must come from within, and the mechanisms for achieving that attitude may be understood by us if we have a sense of history. The answers are before us and it is a matter of our utilizing them.

Those physicians and teachers handling young children might do well to participate with parents in the way that young children are managed according to the principles of human nature derived from history and described by social and biologic psychologists. A medical literature needs to be made available to physicians handling children and adults that will serve as a reservoir of knowledge and as a guide for counseling. Decisions need to be made by organized medicine, and promulgated by the more rigid medical systems that are sure to be upon us, in regard to the possible need for physicians in attendance in homes, for community nurses and for neighborhood infirmaries, and perhaps for a gradual return of medical practice, both technical and psychological, to a much more personal and understandable plane.

If, as I believe, the overwhelming weight of human misery and disease begins in the mind and the attitude, personal and societal, then much more attention must be placed on understanding that. This applies to all branches of medicine working together. It is not as if technical knowledge need be relegated to a secondary level, since it is unlikely that perfection will be obtained and in all likelihood disease is with us to stay. But I do agree that the emphasis should be upon health, upon making people aware of themselves and their responsibilities toward themselves and how to help themselves so that gradually each of us will learn to need a physician rarely and to depend upon himself, his community and his family to maintain himself. Only by understanding how human beings really work, and what human nature really is, can we hope to succeed in participating as physicians in our great opportunity and responsibility for improving the quality of life.

Refer to: Lewis PM: Human nature and the quality of life, *In* Medicine and the quality of life—A forum. West J Med 125:163-164, Aug 1976

LETTERS *to the Editor*

Prisoner Volunteers

To the Editor: Twenty-eight years ago I spent six months in a Federal prison doing research for the National Institutes of Health using "prisoner volunteers" as subjects. After six months of asking myself whether a prisoner really could be a volunteer, I decided I could not answer the question satisfactorily and asked for a transfer. My bias told me that a prisoner could not be a volunteer; only a free man could be a volunteer. That was my bias then and that is my bias now.

Until the question, "Can a prisoner be a volunteer?" is answered there are no pros and cons to measure, as Dr. White and his Committee on Evolving Trends in Society have so heroically attempted. (West J Med 124:514-516, Jun 1976). With the central question unanswered such efforts as theirs are futile.

The mistake is made by assuming that one is dealing with a balance sheet where one can add and subtract and arrive at a valid result. The moral question is not an adder or subtracter the way safety and significance of experiment, adequacy of informed consent and many other factors are; it is a multiplier. Thus, if my bias is correct all factors are multiplied by zero and their relative sums are meaningless.

Because we are rational people we tend to distrust gut feelings. We believe we can measure matters and decide what is right and what is wrong. I believe we should trust gut feelings in moral issues and act accordingly. In the instance of prisoner volunteers, until the question of whether they *can* be volunteers is answered, experiments on them will always carry a taint, a question, an imperfection which doesn't exist when one experiments on free man.

As long as this is so I say don't do it. Act as if the gut feeling is right—however unanswerable it may seem—and don't do it.

Philosophers, jurists, moralists or politicians may some day prove that a prisoner can indeed be a volunteer in the framework of what we seek to have as a good society, and when they do we can pick up where we left off.

David Leigh Rodgers, MD
San Francisco

Management of Lung Abscess

To the Editor: I read with interest the Medical Staff Conference on Lung Abscess (West J Med 124:476-482, Jun 1976) and the accompanying editorial on the same subject by Dr. Finegold (West J Med 124:494-496, Jun 1976). The comments by Dr. Murray and Dr. Finegold were most illuminating, particularly concerning the pathogenesis, bacteriology and antibiotic treatment of the disease. I must say, however, that I was disappointed in the management of the patient, particularly early in the course of his disease, and the fact that neither Dr. Murray nor Dr. Finegold commented on these shortcomings.

All that glitters is not gold, all that wheezes is not asthma and all that cavitates is not tuberculosis. I do not believe that the presence of a positive skin test for tuberculosis in a patient with a cavitary lesion of the lung is enough evidence to treat him with antituberculous medications alone for a four-week period of time. Early bronchoscopy with brushing and biopsy, along with anaerobic as well as aerobic cultures for fungi and acid-fast bacilli, should have been performed at the outset. Even after the patient was admitted to the University of California Hospital he was treated for almost two weeks with intravenous penicillin alone without further bacteriologic studies or bronchoscopy.

Pyogenic lung abscess is a serious disease, the treatment and prognosis of which have changed remarkably in the antibiotic era. I agree with Dr. Murray that "surgical operation is rarely carried out" if he means that open drainage or resectional surgery are rarely indicated. However, bronchoscopy should be performed early in every patient with lung abscess both for diagnostic and therapeutic purposes.

Flexible fiberoptic bronchoscopy has been a significant advance in the management of patients with lung abscess. On three occasions recently we have been able to enter a lung abscess with the flexible bronchoscope or with a suction catheter passed through it and have aspirated up to 50 ml of pus for cytologic, bacteriologic and fungal studies. In this manner transbronchial drainage has been established and excellent material has

been obtained for study to establish the etiology of the abscess.

Dr. Finegold mentions that "direct lung puncture is more hazardous in adults than transtracheal aspiration." I would like to go further and condemn the use of this procedure in lung abscess. I believe that there is a real chance that seeding of the pleural space with microorganisms may occur following such a procedure and, even worse, a persistent bronchopleural fistula may be established. Unfortunately, we have seen the latter occur recently in our hospital.

Again I would like to commend the authors for their discussion but urge the early, aggressive and even repeated use of bronchoscopy in patients with lung abscess. Although antibiotics have changed the picture of pyogenic lung abscess to a significant degree their use does not obviate the necessity for specific bacteriologic information, establishment of proper drainage pathways and general supportive care of these patients.

JAMES B. D. MARK, MD
Professor and Head
Division of Thoracic Surgery
Stanford University Medical Center
Stanford, California

* * *

Dr. Murray Replies

TO THE EDITOR: Dr. Mark's letter raises some interesting and controversial points concerning the role of bronchoscopy in patients with lung abscess. In my opinion, bronchoscopy is useful in these patients under two different circumstances: as an aid in diagnosis and as an ancillary means of managing the patient.

First, bronchoscopy is a time-honored and valuable procedure in patients with a wide variety of pulmonary lesions of uncertain origin, including lung abscess. Furthermore, the diagnostic yield from bronchoscopy has been magnified considerably in recent years owing to the increased range of observation and access available to the fiberoptic instrument. But if the specific cause of a lung abscess has been established by other methods, and there are no unusual features to the patient's illness (for example, an abscess in an edentulous person, suspicion of foreign body or bronchogenic carcinoma), bronchoscopy is not warranted simply because an abscess is present. This recommendation certainly is true for lung abscesses caused by necrotizing infections such as tuberculosis and coccidioidomycosis and, I believe also holds true for pyogenic lung abscesses caused by anaerobes, staphylococci or klebsiella. Once the diagnosis is made by Gram stain and culture and appropriate antimicrobial therapy instituted, the great majority of patients with lung abscess from necrotizing infections will recover without ever having been bronchoscoped.

The value of bronchoscopy as a means of obtaining secretions is probably not as reliable as implied by Dr. Mark. The limitations of the procedure, which were touched on by Dr. Finegold, have been confirmed by a recent article.[1]

Second, bronchoscopy is useful as a means of promoting drainage of abscesses, especially if a catheter can be inserted into the cavity. Thus we perform bronchoscopy in patients with lung abscess who demonstrate signs of retention of pus in the cavity (persistent fever, leukocytosis, systemic toxicity and a fluid level) five to ten days after antimicrobial therapy has been started. Material is obtained for culture and airway obstruction is looked for, but the procedure is chiefly to get rid of pus. When effective, we have no hesitation in repeating bronchoscopy, as recommended by Dr. Mark, as often as needed.

These policies were carried out in the patient under discussion who was bronchoscoped, as stated in the protocol, while he was being followed as an outpatient with suspected tuberculosis. Later, after he was hospitalized and failed to respond to nine days of penicillin therapy, another bronchoscopy was recommended but the patient signed out against advice. He could have been bronchoscoped during his admission to the University of California Hospital but his prompt response to clindamycin made this unnecessary.

JOHN F. MURRAY, MD
Chief, Chest Service
San Francisco General Hospital
Professor of Medicine
University of California, San Francisco

REFERENCE

1. Bartlett JG, Alexander J, Mayhew J, et al: Should fiberoptic bronchoscopy aspirates be cultured? Am Rev Resp Dis 114:73, 1976

* * *

Dr. Finegold Replies

TO THE EDITOR: I appreciate the opportunity to read and respond to the letter by Dr. Mark.

I certainly agree that early, and even repeated, bronchoscopy can be a valuable diagnostic and therapeutic tool, as he has stressed. In the particular patient discussed in the June Medical Staff Conference, it should have been clear on clinical grounds (as discussed by Dr. Murray and me)

that the patient had an anaerobic lung abscess. The only question diagnostically was related to the possibility of an associated condition such as foreign body, tumor or tuberculosis. Bronchoscopy, of course, can be helpful in ruling out such possibilities as well as in effecting adequate drainage. It is important to note, however, that fiberoptic or other bronchoscopy is not suitable for obtaining specimens for culture of bacteria (particularly anaerobic bacteria) other than Mycobacterium since it is not possible to avoid "contamination" of the specimen with resident or transient bacterial flora from the upper respiratory tract. Potential aerobic or facultative pathogens are found with some frequency in the upper respiratory tract flora and anaerobes are universally present there. Furthermore, the local anesthetic used (often in relatively large volume) during bronchoscopy is inhibitory to many bacteria. Whether quantitative bacteriological studies of material obtained through a bronchoscope with appropriate covering sleeve technique would permit distinction between resident and infecting flora has not yet been determined.

SYDNEY M. FINEGOLD, MD
Chief, Infectious Disease Section
Wadsworth Veterans Administration Hospital Center, Los Angeles
Professor of Medicine
University of California, Los Angeles School of Medicine

More on Physician Extenders

TO THE EDITOR: In answer to the letter opposing the physician extender concept by Eugene Felmar, MD, Granada Hills, California [West J Med 24:509, Jun 1976]. The Medex, physician's assistants and nurse practitioners were never intended to replace the service of the MD, but were intended to extend the doctor's capacity of practice and allow him to spend more time with those patients with critical problems. The training of these new medical entities and the services they provide is far from "cut-rate." Was Dr. Felmar on the battlefields of Vietnam when soldiers entrusted their lives to "those barefoot physicians"? Has he responded to the needs of the farm workers of the Salinas Valley who are unable to afford medical care? Has he visited the Indian Reservation Clinics of Arizona and New Mexico, where uneducated people don't even know the meaning of prenatal care? These new medical entities were developed to implement these services and care in areas where physicians are scarce or nonexistent, as the monetary compensation is grossly unsupportive.

Regarding Dr. Felmar's statement that ". . . we are embarking on a two level highway; on the upper highway will be university-trained physicians who will deliver health care to the affluent and probably the politicians and on the lower level will be nurse practitioners and paramedics and/or midwives who will deliver health care to the community." The NP's, Medex and PA's also have had college training, internships and board certification, which Dr. Felmar has failed to note.

No one is asking Dr. Felmar to accept the responsibility for these new practitioners, but is he willing to accept the responsibility for the health care needs of the poor and uneducated? It is beyond my comprehension how any reasonably aware person can discount the good these new paraprofessionals have done in the extension and resolution of the health care needs of people who are grateful to receive their help.

Dr. Felmar should speak to the supervising physicians employing the Medex, NP's and PA's, and see these practitioners at work before passing judgment.

MICHAEL N. ROSOFF, MEDEX, PA
Los Angeles

Improving Quality of Life

TO THE EDITOR: The Congresses on Improving the Quality of Life sponsored by the American Medical Association in 1971, 1972 and 1973 were actually diagnostic exercises. Many of those attending came to the meetings believing that they were to hear about and assist in the discussions of the role of the medical profession in improving the quality of life. Instead the discussions were aimed at dissecting and examining the factors that cause us humans to live a happier and more comfortable life.

Following an accurate diagnosis, improving the quality of life comes naturally. Almost every branch of human endeavor must become involved.

THE WESTERN JOURNAL OF MEDICINE is to be congratulated in pursuing this notable endeavor by conducting the forum on "Medicine and the Quality of Life."

WALTER C. BORNEMEIER, MD
Past President, AMA
Saratoga, CA

Ivan Illich Disputed

To the Editor: It is impossible to grapple on all the requisite levels with all the implications of the ideas advanced by Ivan Illich in his book *Medical Nemesis—The Expropriation of Health* and discussed in the July issue of the Western Journal (Killeen RNF: A review of Illich's *Medical Nemesis* (Editorial). West J Med 125:67-69, Jul 1976).

Illich's basic thesis, as I understand it, is that the institutions of industrial society rob man of his freedom and that modern medicine not only undermines the individual's freedom by leaving him less competent to care for himself but actually constitutes a direct threat to health itself.

One can only come to such a conclusion, it seems to me, by ignoring a considerable body of countervailing evidence.

For instance, Mr. Illich states that in 1976 in the United States, health care offers the most gripping example of the "expropriation of the individual's ability to cope."

How many, I wonder, of the thousands upon thousands of patients freed from mental institutions by the use of tranquilizers and restored to useful, coping lives would argue with that statement?

Are the thousands spared the ordeal of iron lungs or crippled limbs by polio vaccine less free than they would have been without the intervention of modern medicine?

Are those who have been relieved of pain and restored to full mobility by joint-replacement operations less free?

To suffer unnecessary pain or impairment is not coping; it's stupidity. The purpose of medicine—and medical intervention—is to solve a patient's problem and to restore the individual to a condition where coping is possible.

Of course there can be abuses—individual, institutional, social. Undoubtedly, there are. And in any great era of progress (such as the last 30 years in medicine) imbalance and distortions develop which must be rectified.

Is medicine capable of harm? Unquestionably yes. Is it capable of restricting freedom rather than enhancing freedom? Yes again.

But is medicine in the United States in 1976 doing more harm than good, is it restricting rather than enhancing freedom? I think the answer, based on any fair weighing of the evidence, is a resounding no.

Malcolm C. Todd, MD
Past President
American Medical Association
Long Beach

Refer to: Adams RM: Attitudes of California dermatologists toward Worker's Compensation—Results of a survey (Government and Medicine). West J Med 125:169-175, Aug 1976

Attitudes of California Dermatologists Toward Worker's Compensation

Results of a Survey

ROBERT M. ADAMS, MD, *Stanford*

A survey-questionnaire on Worker's Compensation sent to 492 California dermatologists produced 268 replies, a recovery rate of 54 percent, representing approximately 10 percent of the practicing dermatologists in the United States. A total of 75 percent replied they treat Worker's Compensation patients; most of the 25 percent who replied they do not gave strong reasons for refusing to assume the care of these patients. The answers to the questionnaire given by the 201 California dermatologists who treat Worker's Compensation patients are tabulated and discussed. Although there exists considerable misunderstanding among physicians, insurance companies and employers on many aspects of Worker's Compensation, the situation is not without hope for improvement. Better knowledge of work procedures, more availability of precise information on the ingredients of work contactants and cooperation among the interested parties should improve the quality of care for these patients in the future.

DISEASE of the skin continues to be considered the most common occupational disease. Evidence of this is found in statistical reports provided by the California State Department of Public Health. These reports have been published annually since the early 1950's, and are compiled from the "Physician's First Report of Injury or Disease" (Figure 1), which must be completed following the initial visits of patients with possible occupationally-related injury or disease. The informaton that they contain provides a useful glimpse into the extent and variety of occupational skin disease in California (Tables 1 and 2).

From the Department of Dermatology, Stanford University School of Medicine.

Reprint requests to: Robert M. Adams, MD, 1300 University Drive, Menlo Park, CA 94025.

Despite the care with which the Department of Public Health prepares these reports, they fail to reflect accurately the incidence of occupational skin disease in California. Whether the figures for total occurrence are too low or too high is unknown; probably they are too low. For example, the cases of many workers with dermatitis are never recorded because they are treated by plant nurses and no time is lost from work. Some of these workers treat themselves, while others consult physicians who never consider the possibility that the disease might be work-related. On the other hand, in a significant percentage of reported cases the patients are later found to have a skin disease unrelated to employment, but an amended report is never filed. The causative agent that is

DOCTOR'S FIRST REPORT OF OCCUPATIONAL INJURY OR ILLNESS

STATE OF CALIFORNIA
AGRICULTURE AND SERVICES AGENCY
DEPARTMENT OF INDUSTRIAL RELATIONS
DIVISION OF LABOR STATISTICS AND RESEARCH
P. O. Box 965, San Francisco, Calif. 94101

Immediately after first examination mail one copy directly to the Division of Labor Statistics and Research. Failure to file a report with the Division is a misdemeanor. (Labor Code Section 6413.5) Answer all questions fully.

A. INSURANCE CARRIER .....

Do not write in this space

1. **EMPLOYER** .....
2. Address (No., St. & City) .....
3. Business (Manufacturing shoes, building construction, retailing men's clothes, etc.) .....

4. **EMPLOYEE** (First name, middle initial, last name) ..... Soc. Sec. No. .....
5. Address (No., St. & City) .....
6. Occupation ..... Age ..... Sex .....
7. Date injured ..... Hour ..... M. Date last worked .....
8. Injured at (No., St. & City) ..... County .....
9. Date of your first examination ..... Hour ..... M. Who engaged your services? .....
10. Name other doctors who treated employee for this injury .....

11. **ACCIDENT OR EXPOSURE:** Did employee notify employer of this injury? Employee's statement of cause of injury or illness:

12. **NATURE AND EXTENT OF INJURY OR DISEASE** (Include all objective findings, subjective complaints, and diagnoses. If occupational disease state date of onset, occupational history, and exposures.)

13. X-rays: By whom taken? (State if none) .....
Findings:

14. Treatment:

15. Kind of case (Office, home or hospital) ..... If hospitalized, date ..... Estimated stay .....
Name and address of hospital .....
16. Further treatment (Estimated frequency and duration) .....
17. Estimated period of disability for: Regular work ..... Modified work .....
18. Describe any permanent disability or disfigurement expected (State if none) .....
19. If death ensued, give date

20. **REMARKS** (Note any pre-existing injuries or diseases, need for special examination or laboratory tests, other pertinent information.)

Name ..... (Type or print) Degree ..... [PERSONAL SIGNATURE OF DOCTOR] .....

Date of report ..... Address (No., St. & City) .....

FORM 5021 (REV 1) *Use reverse side if more space required* D OSP

Figure 1.—Doctor's First Report of Occupational Injury or Illness (Reproduced by permission of State of California Department of Industrial Relations, Division of Labor Statistics and Research).

recorded on the First Report is often the worker's opinion only; after further investigation, a quite different causative agent may be found.

In a recent study of occupational disease in small businesses in Washington and Oregon, conducted by the University of Washington for the National Institute for Occupational Safety and Health, it was discovered that of 346 conditions of probable occupational origin, only 18 percent were skin disease, which trailed behind hearing loss (28 percent), and respiratory conditions (25 percent). On the other hand, almost 90 percent of the job-related health problems were not reported as occupational disease either on worker's compensation claims or on records kept by employers for the Occupational Safety and Health Administration.[1]

The Worker's Compensation Law in California was enacted in 1913, and since then most physicians have supported and cooperated with its provisions, although often with reluctance. Primary care physicians, such as family physicians, surgeons and internists, treat most of the patients with skin disease, while dermatologists are usually referred more difficult cases, evaluate disputed claims and carry out most of the investigative procedures such as patch testing and plant inspections.

TABLE 1.—*Reports of Occupational Skin Disease, California, 1973*

Total cases	15,671
No time lost	10,474
Time lost	2,788
1-7 days	2,001
8-14 days	435
15 and over	231
Indefinite	121
Not stated	2,409

TABLE 2.—*Occupational Skin Disease Causal Agent, California, 1973*

	Cases
1. Poison oak	3,637
2. Water, soaps, detergents and other cleaning agents	982
3. Solvents	880
4. Plastics	792
5. Petroleum products, not used as solvents	603
6. Glass dust	572
7. Agricultural chemicals	428
8. Acids	426
9. Plant and animal products	391
10. Fruits, nuts, vegetables	382
11. Unspecified dust	258
12. Metals and compounds (other than chromium)	220
13. Food products (other than 10)	210
14. Cement, mortar, plaster	207
15. Cutting oils	206
16. Paints	180
17. Glues, pastes, adhesives	175
18. Medicines, and disinfectants	151
19. Caustics	102
20. Heat, cold, humidity, and other environmentals	98
21. Infections	64
22. Chromium	58
23. Ionizing and other radiation	1
24. Other and unspecified	2,731

In order to learn more about the current attitudes of California dermatologists toward Worker's Compensation, in the fall of 1974 a questionnaire was sent to 492 dermatologists, representing the Fellows and Associates of the American Academy of Dermatology who list their practices in California. It was hoped these practicing dermatologist would share their opinions regarding Worker's Compensation Law, as well as the many and diverse problems presented by patients, insurance companies and employers. By February 1, 1975, 268 replies were received, a rate of recovery of 54 percent. With 2,944 dermatologists listed in private practice in the United States in 1972, the respondents comprise approximately 9 percent of the total number of practicing dermatologists in the United States.

The questions and a tabulation of replies and discussion follow.

1. *Do you treat worker's compensation patients?*
Yes: 201 (75 percent); No: 67 (25 percent)

2. *If not, why not?*
A total of 25 (9 percent) replied negatively because of type of practice (academic, hospital, military or clinic practice). Several respondents had retired and were no longer in practice. Those dermatologists in full-time hospital or military practice undoubtedly treat patients with occupationally-related skin disease, but fail to consider work relationship important.

In all, 42 (15 percent) stated they do not treat worker's compensation cases because they object to one or more features of the practice. Thirteen stated the fee schedule was too low; eleven claimed the paper work excessive; five wrote of "hassles" involved, and four decried "troublesome patients" and "conflicts of interest." Three stated they were never referred these patients, and six gave no reasons. It seems likely that most of the remaining 224 dermatologists who failed to return the questionnaire share several of the above views.

3. *If so, approximately how many new and presumed worker's compensation patients do you see each week?*
1 to 5: 148 (74 percent); 5 to 10: 6 (3 percent); greater than 10: 1 (0.5 percent)

Forty-six (22.5 percent) added another category, suggesting they actually see less than one per week.

4. *How many of the above turn out to be nonoccupational?*

Under 24 percent: 101 (50 percent); 25 to 50 percent: 68 (34 percent); over 50 percent: 18 (9 percent)

No answer: 14 (7 percent)

These figures probably reflect the prevailing opinion among dermatologists that approximately 25 percent of patients who initially are thought to have occupational skin disease are later found to have conditions unrelated to their occupation. It is unlikely that any of the physicians actually reviewed or tabulated their records before answering this question.

5. *Please check (in order of frequency) the industrial sources of your worker's compensation patients:*

Manufacturing	First
Services	Second
Construction	Third
Agriculture	Fourth
Health	Fifth

No answer: 14

Although agriculture is California's principal industry, dermatologists place it fourth as a source of occupational skin disease. This may be explained by the fact that most dermatologists have urban rather than rural practices.

6. *What is the most common occupational skin disease you see?*

All but one respondent stated contact dermatitis, irritant dermatitis, dermatitis venenata, poison oak, or a variation. One physician stated chronic paronychia to be the most common occupational skin condition in his practice.

Fourteen specified one or more of the following: cement, chromates, cutting oils, degreasers, epoxies and other resins, hydrofluoric acid, formalin, color developers, irritation leading to psoriasis, and even strawberries.

7. *What percentage of your worker's compensation cases are the following:*

(1) Contact dermatitis due to irritation? >50 percent: 124; <50 percent: 61

(2) Contact dermatitis due to allergic sensitization? >50 percent: 58; <50 percent: 128

(3) Other skin conditions? (infections, granulomas, tumors and so on) >25 percent: 18; <25 percen: 116

8. *Do you patch test your patients with occupationally-related dermatitis?*

Yes: 186 (93 percent); No: 11 (5 percent); No answer: 4 (2 percent)

This latter question produced the largest number of affirmative answers, indicating a widespread interest in the patch test as a diagnostic tool, and probably represents a significant increase in interest over that prevailing 15 to 20 years ago. The greater emphasis placed on contact dermatitis in dermatology teaching institutions, in journals of dermatology and allergy, at medical meetings and by organizations such as the North American Dermatitis Research Group undoubtedly largely is responsible for the growing number of dermatologists who regularly use patch testing in their practices.

9. *If so, what percentage?*

Over 50 percent: 111 (55 percent); under 50 percent: 50 (25 percent); no answer: 40 (20 percent)

The large percentage of patients patch tested represents those suspected of allergic contact dermatitis rather than irritant dermatitis, which is not investigated by patch testing. The question, however, was not as clear as it should have been.

10. *Do you use any of the following patch test materials:*

Hollister-Stier	58
Johnson and Johnson	24
Combination of above	46
Trolle-Lassen	9
A combination of above	27
Work materials only	5
None	14
No answer	18

Only 9 respondents state they use the patch test materials from the Trolle-Lassen Laboratory in Denmark, which has the most complete selection of patch test chemicals available anywhere.

11. *Are you satisfied that patch testing provides you with useful information in the handling of worker's compensation patients?*

Yes: 146 (73 percent); No: 42 (21 percent); No answer: 13 (6 percent)

12. *If not, why not?*

The dermatologists who answered this question gave a variety of reasons for their dissatisfaction with patch testing. The most common were (1) difficulty in correlation of positive results with the work carried out; (2) suspicion of false negative reactions; (3) inability to duplicate actual work conditions during testing; (4) irritant reactions when testing with substances as used in the work; (5) problems of dilution; (6) spoilage of test materials.

13. *How could patch testing be made more practical in your practice?*

Many of those who answered this question desired a greater range of test materials available, with more accurate information on where they are found, especially ingredients of trade-named products. Several wanted more educational materials, and a number suggested the establishment of "patch test banks" in medical schools where patients could be referred for more detailed study.

14. *What could the employer and/or worker's compensation carriers do to further assist you in the care and rehabilitation of these cases?*

Most of the respondents wanted a more realistic fee schedule, better cooperation between physician and insurance personnel, additional and more detailed information on working techniques and the chemical components of their patient's work contactants. Many dermatologists complained that when dermatitis develops, employers transfer workers to lower-paying positions, or summarily discharge them.

15. *In your opinion, is the incidence of occupational disease becoming:*

(1) More frequent: 25 (12 percent); (2) Less fre-

quent: 23 (11.5 percent); (3) Staying the same: 130 (65 percent); No answer: 23 (11.5 percent)

16. *Do you regularly treat patients referred from any particular plant or factory?*

Yes: 74 (37 percent); No: 119 (59 percent); No answer: 8 (4 percent)

17. *Are you a "panel" physician?*

Yes: 30 (15 percent); No: 143 (71 percent); No answer: 28 (14 percent)

18. *Please check the size of the community or metropolitan area in which you practice:*

Under 10,000: 0; 10,000 to 20,000: 3 (1 percent); 20,000 to 50,000: 28 (14 percent); 50,000 to 100,000: 44 (22 percent); Over 100,000: 110 (55 percent); No answer: 16 (8 percent)

With 82 percent of the respondents practicing in communities of 50,000 persons or more, it appears that dermatologists, along with other physicians, prefer to practice in urban areas.

19. *Are you satisfied with the fee schedule for worker's compensation cases?*

Yes: 89 (44 percent); No: 90 (45 percent); No answer: 22 (11 percent)

20. *Any further comments, please:*

64 did (32 percent)

Most of the comments were a variation or a reemphasis of answers given to question 14.

21. *Signature:*

142 did; 59 did not

Discussion

Physicians who object most strongly to "third party" interference in patient care are often those who find worker's compensation cases the most odious. However, Worker's Compensation Law goes a step further, and adds a "fourth party" with whom physicians must frequently contend: the employer. The necessity to deal with both insurance companies and employers, lower-than-standard fees, extra paper work and occasionally uncooperative or hostile patients, creates an intolerable combination for many physicians.

The situation is not hopeless, which the results of the survey seem to indicate. More than half of those dermatologists who were sent questionnaires responded (54 percent), which in itself indicates a definite stand one way or another. Of those who did take the time to answer, 75 percent stated they do treat worker's compensation patients, and many offered positive, constructive recommendations.

Physicians who complain about the interference of insurance companies and employers should understand that the patient-physician relationship is not entirely private under worker's compensation law. Insurance carriers and employers both have understandable legal rights in the matter. Soon after each occurrence, the insurance company *must* receive from the attending physician information regarding the diagnosis; the nature and extent of anticipated, temporary and permanent disability, and the plan of treatment. Without this information, the underwriter cannot build a cost-projection for that injury or disease and begin rehabilitation efforts when necessary. The insurance company also has legitimate interest in the quality of the care and its cost, and when dissatisfied with the care, may recommend that the patient change physicians. It also has the legal right to demand prompt reports; a frequent complaint of insurance personnel is the slowness with which many physicians submit their reports. On the other hand, physicians justifiably complain about the tardiness with which many carriers process and pay undisputed claims. It is often found that a claim is simply "shelved" because of incomplete information which a telephone call could help resolve.

Because fees vary so widely, "usual and customary" fees are obviously impractical when insurance carriers must plan for future losses. Although there is no doubt that for years worker's compensation fees lagged behind the average physician's charges, the new rate schedule which became effective October 1, 1974 was quite close to the fees charged by most dermatologists in metropolitan areas of California at that time. Physicians often forget, however, that the fees are based upon a minimum fee schedule and insurance carriers will pay any reasonable fee which can be justified by the circumstances. For example, if extra time is required, the insurance carrier will reimburse the physician, but he must show the extra service on the Relative Value Studies (RVS) code, and a narrative report will usually be required. If the patient is referred from another physician, the visit may be considered a consultation. For patch testing, an office visit plus the usual RVS charges for patch testing may be used. Even plant visits are compensable, if requested by the company or insurance carrier, and *prior* authorization is obtained. Such visits are especially valuable to the insurance carrier if the physician's report leads to a safer environment within the plant and fewer claims. Even the services of an industrial hygienist may be made available if they are requested by the carrier.

Excessive paperwork is a frequent complaint. Duplicate copies of the "Physician's First Report" or a more detailed report are legally required to be submitted, immediately following the initial visit, to insurance carrier and the Division of Industrial Safety. As a courtesy, the physician may send a copy to the employer. For subsequent visits, brief supplementary reports must also be filed. The "Physician's First Report" is simple and brief (Figure 1), and contains only basic information. The space provided for description of the work and the nature of the illness is inadequate. For this reason many dermatologists attach a separate report in which the work is described in detail, as well as the substances contacted, the history of the dermatitis, the results of special tests, diagnosis, prognosis, disability and recommendations for treatment and prevention. This provides much more useful information for the insurance company and employer than that contained in the "First Report." If a work relationship is uncertain at the first visit, the dermatologist should state this and suggest the measures necessary to reach a definite decision. Carriers will pay for such investigation until a diagnosis can be reached. If the patient is disabled and the carrier refuses to acknowledge liability, disability payments can be paid from state disability funds and a lien established against the worker's compensation carrier until the case is decided one way or the other, as in disputed cases by the Appeals Board referee.

The "fourth party," the employer, pays the premiums for coverage as required by law, and at a rate determined by his worker's compensation accident and illness experience during the previous year. This method of rate determination was instituted many years ago and emphasizes to the employer the necessity of maintaining safe working conditions and of educating workers in the proper handling of hazardous substances. If a copy of the "Physician's First Report" is sent to the employer, it should state not only the nature of the dermatitis, but also a description of the contributing factors. With this information the employer can consider removal of hazardous materials from contact with workers' skin (through changes in the work processes or techniques of handling) or at least mitigation of the irritating or sensitizing effects through protective measures.

Since enactment of the Occupational Safety and Health Act in 1970, employers have been more cooperative with physicians in providing information regarding plant operations and the ingredients of industrial products. Dermatologists who treat even an occasional patient from a particular plant should arrange to visit the plant, inspect the work areas and discuss the skin hazards with the personnel. Such visits rarely take more than an hour or two, but they can provide a physician with invaluable insight into the activities and hazards of a plant, as well as enabling him to better evaluate future patients' descriptions of their work.

A frequent suggestion is that patch test materials for all industrial contactants should be readily available and inexpensive. A bank of test substances for each of the 35,550 job titles in 21,741 separate occupations[1] cannot be accomplished, for obvious reasons. Thousands of chemicals are used in industry, but only several hundred are definitely known to be contact allergic sensitizers. Many of them are disguised under a trademark, often in combination with other ingredients. It is a formidable and discouraging task confronting the physician who attempts to learn the exact ingredients of industrial products. Persistence and devotion are required; few dermatologists have the time or interest to follow the investigation to completion. However, several texts are available[3-9] to assist dermatologists in learning the ingredients of industrial products. The local Poison Control Center can be immeasurably helpful, not only in providing information on ingredients, but also in supplying telephone numbers of manufacturers, including the names of key persons to contact. The text *Toxicology of Commercial Products* by Gleason, Goslin, Hodge and Smith[9] contains much useful information on ingredients and should be owned by every dermatologist who does patch testing. The local health department, especially if there is a division of occupational health, can be of great assistance, particularly in finding out the previous dermatitis experience of a particular plant or industry, in obtaining information about industrial processes and the ingredients of products, and in helping to develop rapport with the personnel of local industries. Until recently, a copy of each "Physician's First Report" was sent to the occupational health personnel of the county in which the event occurred, keeping these personnel informed of the work hazards of industries in their area, and providing an opportunity for prevention of similar occurrences. Unfortunately this practice was discontinued in 1974, because of lack of funds.

A frequent complaint is that employers simply

discharge workers who must change their jobs because of a disabling dermatitis. If the worker's illness does not require him to leave work entirely, too often he must accept another job at greatly reduced income. Employers in small plants especially, have no choice other than to discharge workers with recurring dermatitis, but California's new rehabilitation law, Assembly Bill 760, enacted on January 1, 1975, may correct some of the inequities, especially if it is properly funded and implemented. Dermatologists can be of immeasurable assistance in the rehabilitation of disabled workers, not only by indicating its necessity but by discussing job alternatives with employers and insurance carrier representatives, and also, in the case of allergic sensitization, clearly stating the permissible occupations in which contact with the patient's sensitizers is unlikely to occur.

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Minidose Heparin Prophylaxis for Prevention of Pulmonary Embolism

The simplest and the most generally applicable method of prophylaxis (before surgical operation) involves drug treatment with various agents designed to prevent hypercoagulability. Agents that have been tested . . . include low dose heparin. In a large series of studies on low dose, preoperative, perioperative and postoperative heparin therapy, in almost all cases a significant protection against peripheral venous thrombosis has been shown. Since venous thrombosis might develop during the day of operation, and one day thereafter, treatment must begin before the operative procedure. In spite of this, bleeding has not been reported as a problem. The standard minidose or small dose heparin prophylaxis is 5,000 units two times a day. . . . Published evidence and clinical experience now indicate that low dose heparin prophylaxis be recommended as primary prevention for all adults in whom major abdominal, pelvic or thoracic surgical procedures are carried out. . . . A standard regimen fulfills most of the criteria demanded of an ideal prophylactic agent. It is well tolerated by the patient, it is free of side effects and it requires no monitoring other than seeing that the patient receives the drug appropriately. It does not produce excessive bleeding when the patient is subjected to major tissue trauma.

Now, I can agree in general with these observations, but with some qualifications. First of all, I am not entirely satisfied that the bleeding problem has been looked at in as much depth as it should be, particularly in terms of morbidity—like late wound complications and actual surgical blood loss. Most of the reported lack of bleeding difficulty is based on observations by the surgeons which are not necessarily quantitative. On the other hand, it is now possible to identify very high risk groups, and I think the data now are so hard that certainly in patients who fall into a high risk group, minidose heparin prophylaxis should be used on the basis of the current knowledge.

—JOSEPH J. McNAMARA, MD, *Honolulu*

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TERRY P. CLEMMER, MD, Salt Lake City
Director, Critical Care Unit, L.D.S. Hospital

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Peer Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Peer Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Peer Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Repository Emulsion Therapy

QUESTION:

Is repository emulsion therapy in the treatment of allergy conditions considered accepted medical practice? (Asked by Blue Shield of California)

OPINION:

In the opinion of the Advisory Panel on Allergy, repository emulsion therapy has not proved to be of sufficient benefit to be recommended.

Electroshock

QUESTION:

What are the medical indications and contraindications for electroconvulsive therapy? (Asked by Peer Review Commission, California Medical Association)

OPINION:

In the opinion of the Advisory Panels on Psychiatry and Neurology, electroshock therapy is a well-established treatment for certain psychiatric disorders. It is principally used in cases of severe depression—depression unresponsive to psychotherapy or medication, or which is life-threatening and requires immediate intervention. Acute schizoaffective schizophrenia is commonly treated by electroshock, as are catatonia, involutional states such as melancholia and manic conditions. Respondents mentioned that shock therapy would be the treatment of choice in many cases —not necessarily second to other methods of management.

Electroshock therapy would be contraindicated in patients with increased intracranial pressure (a brain tumor, for example) or a recent myocardial infarction. Other conditions which, depending on the patient and the necessity for therapeutic intervention, might be contraindications include hypertension, tuberculosis, skeletal or seizure disorders, and psychoneuroses.

Examination of Orthopedic Hardware

QUESTION:

(1) Would good medical practice require that surgically removed orthopedic hardware be routinely sent to the pathology laboratory for examination? (2) Is it customary for a patient to be charged for the above examination? (Asked by the Hospital Council of Northern California)

OPINION:

In the opinion of the Advisory Panels on Pathology and Orthopedics, it is customary medical practice for surgically removed orthopedic hardware to be sent to the pathology laboratory for examination. Most members of the panels felt that this practice is part of proper record keeping, but that routine examination of the material rarely provides medically important information.

Nearly all respondents agreed that a small charge for the examination is customary and reasonable.

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 22 recognized specialties of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

in memoriam

Benninger, Charles, jr., Oroville. Died September 26, 1975 of cancer of the prostate, aged 76. Graduate of Cornell University Medical College, New York City, 1931. Licensed in California in 1931. Dr. Benninger was a retired member of the Butte-Glenn Medical Society.

Biedermann, George A., Daly City. Died October 29, 1975 in Daly City of heart disease, aged 56. Graduate of Ludwig-Maximilians-Universität Medizinische Fakultät, München, Bavaria, 1947. Licensed in California in 1953. Dr. Biedermann was a member of the San Mateo County Medical Society.

Churchill, Asa Glenn, San Rafael. Died May 10, 1976 in San Rafael, aged 79. Graduate of the University of Minnesota Medical School, Minneapolis, 1921. Licensed in California in 1932. Dr. Churchill was a retired member of the San Francisco Medical Society.

Cohen, Milton Robert, Los Angeles. Died June 19, 1976 in Los Angeles, aged 58. Graduate of the University of Texas School of Medicine, Galveston, 1942. Licensed in California in 1947. Dr. Cohen was an associate member of the Los Angeles County Medical Association.

Dolfini, Walter William, Eureka. Died April 23, 1976 in Eureka of carcinoma, aged 67. Graduate of McGill University Faculty of Medicine, Montreal, 1936. Licensed in California in 1937. Dr. Dolfini was a retired member of the Humboldt-Del Norte Medical Society.

Drees, Lawler Adolph, Petaluma. Died June 5, 1976 in Calistoga, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Dr. Drees was a retired member of the San Francisco Medical Society.

Feinberg, Munish, Los Angeles. Died March 23, 1976 of heart disease, aged 68. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1934. Licensed in California in 1934. MD degree from California College of Medicine, 1962. Dr. Feinberg was a retired member of the Los Angeles County Medical Association.

Field, John Bryon, Beverly Hills. Died June 1, 1976 in Beverly Hills of myocardial infarction and diabetes mellitus, aged 57. Graduate of the University of Rochester School of Medicine and Dentistry, 1948. Licensed in California in 1951. Dr. Field was a member of the Los Angeles County Medical Association.

Freilich, Myron A., San Mateo. Died May 6, 1976 in San Mateo, aged 67. Graduate of the University of Cincinnati College of Medicine, 1937. Licensed in California in 1954. Dr. Freilich was a member of the San Mateo County Medical Society.

Goddard, John Lee, Inglewood. Died October 13, 1975 in Long Beach of complications of a surgical operation, aged 43. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1957. Licensed in California in 1958. Dr. Goddard was a member of the Los Angeles County Medical Association.

Groenke, Charles Burkholm, Livermore. Died April 23, 1976 in Livermore of heart disease, aged 56. Graduate of the University of Illinois College of Medicine, Chicago, 1944. Licensed in California in 1948. Dr. Groenke was a member of the Santa Clara County Medical Society.

Hansen, Phil, Long Beach. Died April 19, 1976 in Los Angeles of complications of gall bladder operation, aged 66. Graduate of Washington University School of Medicine, St. Louis, 1939. Licensed in California in 1944. Dr. Hansen was a retired member of the Los Angeles County Medical Association.

Higger, Harvey L., Anaheim. Died October 3, 1975, aged 44. Graduate of the University of Chicago, The School of Medicine, 1957. Licensed in California in 1958. Dr. Higger was a member of the Orange County Medical Association.

Jones, Louis Ernest, Roseville. Died May 23, 1976, aged 76. Graduate of St. Louis University School of Medicine, 1928. Licensed in California in 1928. Dr. Jones was a member of the Placer-Nevada County Medical Society.

Kaplan, Marvin, Canoga Park. Died May 27, 1976 in Northridge of melanoma, aged 54. Graduate of the University of Buffalo School of Medicine, 1951. Licensed in California in 1952. Dr. Kaplan was a member of the Los Angeles County Medical Association.

Lagonegro, John H., Hayward. Died May 13, 1976 in Union City, aged 56. Graduate of Marquette University School of Medicine, Milwaukee, 1944. Licensed in California in 1955. Dr. Lagonegro was a member of the Alameda-Contra Costa Medical Association.

Meland, Orville N., Los Angeles. Died January 27, 1976 in Los Angeles, aged 86. Graduate of the University of Minnesota Medical School, Minneapolis, 1913. Licensed in California in 1926. Dr. Meland was a member of the Los Angeles County Medical Association.

Molony, William R., sr., Los Angeles. Died June 18, 1976, aged 97. Graduate of the College of Medicine of University of Southern California, Los Angeles, 1901. Licensed in California in 1901. Dr. Molony was a past president of the California Medical Association and of the Los Angeles County Medical Association, and a member of the Los Angeles County Medical Association.

MUNK, JIRI GEORGE, Los Angeles. Died April 15, 1976 in Burbank of heart disease, aged 58. Graduate of Deutsche Universität Medizinische Fakultät, Prague, 1946. Licensed in California in 1949. Dr. Munk was a member of the Los Angeles County Medical Association.

NAUHEIM, HERBERT S., Los Angeles. Died May 1, 1976 in Los Angeles of aplastic anemia, aged 75. Graduate of Universität Heidelberg Medizinische Fakultät, Baden, 1923. Licensed in California in 1937. Dr. Nauheim was a member of the Los Angeles County Medical Association.

OLINGER, ALLEN F., Mountain View. Died June 1, 1976 in Santa Clara of heart disease, aged 55. Graduate of New York University College of Medicine, New York City, 1945. Licensed in California in 1948. Dr. Olinger was a member of the Santa Clara County Medical Society.

POPPER, MAX, Los Angeles. Died March 28, 1976, aged 82. Graduate of Medizinische Fakultät der Universität, Wien, 1920. Licensed in California in 1940. Dr. Popper was a member of the Los Angeles County Medical Association.

RAWLINS, AUBREY GATLIFF, San Francisco. Died May 17, 1976 in San Francisco, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Dr. Rawlins was a member of the San Francisco Medical Society.

REAM, MILTON PARKE, Oakland. Died May 25, 1976, aged 74. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1929. Dr. Ream was a retired member of the Alameda-Contra Costa Medical Association.

REYNOLDS, LLOYD R., San Francisco. Died May 31, 1976 in San Francisco, aged 85. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco. 1920. Licensed in California in 1920. Dr. Reynolds was a retired member of the San Francisco Medical Society.

RULIFFSON, HOWARD D., Gilroy. Died June 6, 1976 in Gilroy, aged 61. Graduate of State University of Iowa College of Medicine, Iowa City, 1950. Licensed in California in 1952. Dr. Ruliffson was a member of the Santa Clara County Medical Society.

SCARBOROUGH, ROBERT ALEXANDER, San Francisco. Died May 8, 1976 in San Francisco of heart disease, aged 74. Graduate of Yale University School of Medicine, New Haven, 1926. Licensed in California in 1929. Dr. Scarborough was a member of the San Francisco Medical Society.

SCHMIDT, FRANK MATHER, Los Angeles. Died June 7, 1976 in St. Helena, aged 76. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Dr. Schmidt was a member of the Los Angeles County Medical Association.

SCHUBE, PURCELL GEORGE, Altadena. Died January 24, 1976 in Glendora of heart disease, aged 71. Graduate of the University of Cincinnati College of Medicine, 1929. Licensed in California in 1941. Dr. Schube was a member of the Los Angeles County Medical Association.

SILVER, EMMANUEL, Palo Alto. Died January 5, 1976 in Stanford Hospital of myocarditis, aged 60. Graduate of Tufts College Medical School, Boston, 1939. Licensed in California in 1946. Dr. Silver was a member of the Santa Clara County Medical Society.

STEIN, EDWARD, Stockton. Died May 7, 1976 in Florence, Oregon of injuries received in a light plane crash, aged 41. Graduate of the Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, 1961. Licensed in California in 1963. Dr. Stein was a member of the San Joaquin County Medical Society.

TATRO, RAYMOND F., San Bernardino. Died June 6, 1976 in San Bernardino, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1928. Licensed in California in 1928. Dr. Tatro was a member of the San Bernardino County Medical Society.

THIENES, CLINTON HOBART, Pasadena. Died May 18, 1976 in Pasadena of heart disease, aged 79. Graduate of the University of Oregon Medical School, Portland, 1923. Licensed in California in 1932. Dr. Thienes was a member of the Los Angeles County Medical Association.

ULRICH, CLIFFORD WILLIAM, Whittier. Died April 28, 1976 in Whittier of heart disease, aged 52. Graduate of Northwestern University Medical School, Chicago, 1947. Licensed in California in 1953. Dr. Ulrich was a member of the Los Angeles County Medical Association.

WILLIAMS, ARTHUR JUSTIN, San Francisco. Died May 9, 1976 in San Francisco, aged 74. Graduate of the University of Colorado School of Medicine, Denver, 1928. Licensed in California in 1933. Dr. Williams was a member of the San Francisco Medical Society.

ZOGLIN, STANTON F., Mountain View. Died May 19, 1976 in Mountain View of heart disease, aged 51. Graduate of Harvard Medical School, Boston, 1951. Licensed in California in 1956. Dr. Zoglin was a member of the Santa Clara County Medical Society.

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ORTHOPEDIC SURGEON AND UROLOGIST for Western Colorado eleven man multispecialty group. Established practice close to skiing, hiking, trout fishing, big game hunting and year round Hot Springs swimming pools. Modern clinic facility located next to 40 bed hospital. Contact G. Thomas Morton, MD, Glenwood Medical Associates, 1905 Blake Ave., Glenwood Springs, Colorado 81601.

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ORTHOPEDIC SURGEON (ACADEMIC), to establish a teaching service in a university affiliated VA Hospital. Board certification in orthopedic surgery necessary. Send curriculum vitae and references to Veterans Administration Hospital; 510 E. Stoner; Shreveport, LA 71130.

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(Continued on Page 22)

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Salary to $43,500

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Résumé to:

LOUIS E. MAHONEY, MD, DrPH
Director of Public Health
County of San Bernardino
351 Mountain View
San Bernardino, CA 92415

(Continued from Page 21)

PHYSICIANS WANTED

INTERNIST — Board certified. Prefer subspecialty GI or pulmonary. Join active, prestigious group of three established Internists. Ideal practice, office, hospital, academic and living conditions. Loveliest area of San Francisco Peninsula. Curriculum vitae to Box 1615, San Mateo, CA 94401.

PHYSICIANS WANTED—Well established Medical Community badly needs three Family Practitioners, Two Ophthalmologists, one Dermatologist, one Urologist, and two Pediatricians. Opportunity to set up independent practice in a Medical Community with long established overflow practices. Guaranteed income, Rent Assistance, and generous financing for equipment available. Write: Charles Correll, P.O. Box 7011, Houston, Texas 77008; include curriculum vitae and photo.

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PHYSICIAN—Full-time opening in the Narcotic Abuse Treatment Program. Would be giving examinations and working with illnesses related to the use of narcotics. Involves working with teams in two clinics. California license required, community education experience would be valuable. Contract range $37,000-$40,950. Contact George Wilson, Department of Health, P.O. Box 11867, Fresno, California 93775, or call (209) 488-3055.

INTERNIST: Board Certified Internist wanted to associate with established physician and surgeon; new office facilities in a community with a 60,000 population service area, and excellent outdoor recreation. Please call or write: Alan E. King, MD, 1122 N.W. Garden Valley Blvd., Roseburg, Oregon 97470.

CALIFORNIA—CHIEF OF FAMILY PRACTICE. Hospital in delightful California city, major affiliate of University of California, San Francisco, is seeking an academically-oriented family practitioner to lead innovative, thriving Family Practice Residency Program. Geographic full-time. Professional liability insurance paid. Equal Opportunity Employer. Send curriculum vitae in first letter to: Jerome S. Harris, MD, Director of Medical Affairs, Valley Medical Center of Fresno, 445 So. Cedar, Fresno, CA 93702.

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OCTOBER 2-4, 1976

This three-day residential conference for physicians and clinicians will be held at Asilomar Conference Grounds, Pacific Grove, California, and is sponsored by California State University, Los Angeles and the Fuller Graduate School of Psychology.

Some of the outstanding speakers are: Michael Gazziniga, SUNY-Stonybrook; Earl Pribram, Stanford Medical School; Ralph Reitan, University of Washington; Richard Schain, UCLA Medical School; Jeri Sechzer, New York Hospital; Oliver Zangwill, Cambridge University.

Cost: $100 plus room and board.

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announce

THE SECOND ANNUAL LYMAN A. BREWER III CARDIOTHORACIC SYMPOSIUM

on

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TUESDAY

SEPTEMBER 21, 1976—8:30 am to 6:00 pm

BANQUET 7:00 pm to 10:00 pm (Honored Guest Speaker)

The Los Angeles Hilton, 930 Wilshire, Los Angeles, CA 90017

PROGRAM CHAIRMAN: LOUIS G. LUDINGTON, MD, Associate Clinical Professor of Surgery, Loma Linda University School of Medicine; Chairman, Department of Thoracic and Cardiovascular Surgery, White Memorial Medical Center

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GUEST FACULTY: JAY L. ANKENEY, MD, Professor and Director, Division of Cardiothoracic Surgery, Case Western Reserve University, Cleveland, Ohio

VIKING J. BJORK, MD, Professor and Chairman, Department of Thoracic Surgery Clinic, Karolinska Institute, Stockholm, Sweden

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HAROLD V. LIDDLE, MD, Assistant Clinical Professor of Thoracic and Cardiovascular Surgery, University of Utah School of Medicine, Salt Lake City, Utah

NORMAN E. SHUMWAY, MD, PhD, Professor and Chairman, Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, California

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INFORMATION: Registration Fees: Physicians, $50.00; Residents, Nurses and others $20.00 (Includes luncheon and banquet)

Make checks payable to Lyman A. Brewer III Symposium

Mail to: Department of Thoracic and Cardiovascular Surgery
White Memorial Medical Center
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Los Angeles, CA 90033. Tel. (213) 269-9131, Ext 429 or 535

Credit: This program is approved for 8 hours Category 1 credit in the California Medical Association Certification Program and 8 hours relicensure credit in the California Nursing Association

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DIAGNOSTIC RADIOLOGIST—Board Certified/Eligible, to join as third man in Department of 48 man multispecialty group. Beautiful coastal area. W. Richard Ellis, Administrator, P.O. Drawer LL, Santa Barbara, CA 93102.

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OREGON—Full-time, career oriented Emergency Physicians needed for active Emergency Department in Roseburg area. Direct CV's to Paul Norris, MD, Douglas Community Hospital, 738 E. Harvard Blvd., Roseburg, Oregon 97470.

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NORMAN J. DIAMOND, MD
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FULL AND REGULAR PART-TIME POSITIONS for career-oriented emergency physicians. 40-hour work week, competitive salary, full specialty backup. Excellent fringe benefits including paid malpractice, vacation, educational leave, pension plan. Suburban north San Francisco Bay location. Contact: Paul E. Stange, MD, Kaiser-Permanente Medical Center, 975 Sereno Drive, Vallejo, CA 94590; (707) 644-5631.

STAFF PHYSICIANS needed in innovative multi-specialty group practice being organized for delivery of comprehensive primary patient care. Activities include inpatient care, ambulatory care, and teaching. Equal Opportunity Employer. Write Chief, Medical Service, VA Hospital, Long Beach, CA 90822 or call (213) 498-1313, ext. 2305/2159.

AAFP BOARD ELIGIBLE FAMILY PRACTITIONER for busy two man clinic. Try 6-8 weeks Locum tenens for FP-OB and you'll stay. Need Washington State license. Lynden, WA, 14 miles from hospital, college. Abundant skiing, fishing, sailing. See us on your vacation. L. P. Servid, MD, 1001 E. Front St., Lynden, WA 98264.

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STAFF PSYCHIATRIST—The Fresno County Department of Health has an opening in the Crisis and Out-Patient Services in a community oriented program with emphasis on multidisciplined team services. California license and Board eligibility required. Salary range from $39,955 and up depending on experience. Contact James T. Stripe, MD, Fresno County Department of Health, P.O. Box 11867, Fresno, CA or telephone (209) 488-3731.

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INTERNIST board certified or eligible, CARDIOLOGY preferred as sub-specialty, to join partnership of well established group of internists. Reply with C.V. to R. J. Bartlett, MD, 909 Hyde Street, Suite 125, San Francisco, CA 94109.

(Continued on Page 32)

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Excellent Financial Return
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Beach location in California

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Qualifications include: (1) Eligible for certification of the American Board of Otolaryngology; (2) Medical licensure in California; (3) Surgical skills in all aspects of head and neck surgery; (4) Experience and skill in teaching at undergraduate and postgraduate levels; (5) Knowledge and skill in basic research in otolaryngology; and (6) Experience and skill in administration in an academic environment. Contact:

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Head, Division of Otolaryngology
University Hospital
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INFORMATION

(415) 777-2000

In two separate multicenter studies* of patients with chronic or frequently recurrent urinary tract infections

10 days of Bactrim™ therapy produced better results in maintaining clear cultures than:

- 10 days of ampicillin therapy
- 28 days of cephalexin therapy

*Protocols identical except for drug administered and duration of therapy. Protocol details on last page of this advertisement.

Please see summary of product information on last page of this advertisement.

ROCHE

Roche
Research
U.T.I. Study
No. 2

ne month after therapy ceased, a higher percentage of Bactrim-treated patients maintained clear cultures*.

	No. of patients	Therapy	% of clear cultures*
Study No. 1	80	10-day Bactrim	71.3%
	76	10-day ampicillin	56.6%
Study No. 2	60	28-day cephalexin	56.7%

rite on for clear culture: 1000 or fewer organisms/ml of urine.

ne month after therapy: 10 days of Bactrim maintained ea cultures for one month in a larger percentage of atients than either of the other agents. The maintenance f clear cultures for one month after therapy has ended particular importance for patients whose problems re hronic or recur frequently, for it is during this period ate lapse or reinfection often occurs.

nmediately after therapy: Here again, Bactrim results er superior. At the end of therapy, 90.4% of 83 patients n 1 days of Bactrim had clear cultures, compared with 81.7% of 82 patients on 10 days of ampicillin and 86.6% of 82 patients on 28 days of cephalexin.

Adverse reactions: Side effects in these studies were relatively mild (*e.g.*, nausea, vomiting, rash), but more serious adverse effects can occur with the agents studied. For a complete list of adverse reactions with each drug, please consult the manufacturer's product information.

Note: Bactrim single strength tablets were used in these clinical trials. However, studies have established the bioequivalency of one Bactrim DS tablet with two single strength Bactrim tablets.

Bactrim T.M.
(0 g trimethoprim and 400 mg sulfamethoxazole)
ablets

Bactrim T.M. DS
(160 mg trimethoprim and 800 mg sulfamethoxazole)
Double Strength tablets

For chronic or frequently recurrent cystitis pyelonephritis due to susceptible organisms.

For longer lasting results in chronic or frequently recurrent cystitis or pyelonephritis

Bactrim™

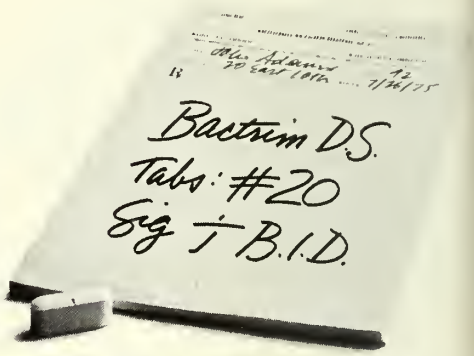
(80 mg trimethoprim and 400 mg sulfamethoxazole)

tablets

Bactrim™ DS

(160 mg trimethoprim and 800 mg sulfamethoxazole)

Double Strength tablets



Protocols

While results came from separate studies, protocols were identical with few exceptions:

Equivalencies: Patients selected were asymptomatic with chronic significant bacteriuria or had suffered a recurrence of previously treated symptomatic disease; significant bacteriuria was established as 100,000 or more of same organisms/ml urine in 2 consecutive cultures within 7 days; patient exclusions for reasons of safety or efficacy were identical; the same baseline laboratory studies were made at the same intervals; identical criteria were used to measure success or failure; clear culture was considered as 1000 or fewer organisms/ml urine.

Exceptions: Drug regimens differed (Study # 1, two Bactrim tablets b.i.d. or one 500-mg ampicillin capsule q.i.d. for 10 days; Study # 2, one 250-mg cephalexin pulvule q.i.d. for 28 days); pretreatment organisms had to be susceptible to ampicillin or cephalexin, but not necessarily to Bactrim.

For more detailed information on the two separate multicenter studies (see previous pages) in which Bactrim achieved better results than ampicillin or cephalexin in maintaining clear cultures, write to:

Professional Services Department
Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections evidenced by persistent bacteriuria (symptomatic or asymptomatic), frequently recurrent infections (relapse or reinfection), or infections associated with urinary tract complications, such as obstruction. Primarily for cystitis, pyelonephritis or pyelitis due to susceptible strains of *E. coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris* and *Proteus morganii.*

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in these urinary tract infections.

The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. **Data are insufficient to recommend use in infants and children under 12.**

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) every 24 hours
Below 15	Use not recommended

Supplied: Double Strength (DS) tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

Oral suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole; fruit-licorice flavored — bottles of 16 oz (1 pint).

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ALCOHOLISM AND DRUG ABUSE

October 16—**Polydrug Abuse.** USC. Saturday.

CANCER

October 6—**Urological Cancer Conference—4th Annual.** Los Angeles Urological Society and American Cancer Society, California Division, at Century Plaza Hotel, Los Angeles. Monday. Contact: William Tanner, L.A. Cancer Society, 2932 Wilshire Blvd., Santa Monica 90403. (213) 828-7474.

October 9-10—**Psychosomatic Approaches to Cancer Therapy.** UC Extension and Gladman Memorial Hospital at UC, Berkeley. Saturday-Sunday. 12 hrs. Contact: Univ. of Calif. Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1064.

October 23—**Symposium on Endometrial Carcinoma.** St. John's Hospital, Santa Monica. Saturday. $30. Contact: James Moran, MD, 2200 Santa Monica Blvd., Santa Monica 90404.

October 29-30—**The Professional Team Approach to Cancer Health Care.** Claire Zellerbach Saroni Tumor Institute, Mt. Zion Hospital and Medical Center, at Hyatt Regency, San Francisco. Friday-Saturday. 11½ hrs. $110 for team (physician and one supportive professional); $85 for physician. Contact: Dept. of Continuing Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. 6 hrs. $100. Contact: CTTR, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

December 29-30—**Clinical Cancer Symposium.** USC. Wednesday-Thursday.

MEDICINE

August 25-27—**Cardiology Today: For the Physician in Clinical Practice.** Mt. Zion Hospital and Medical Center, Univ. of Pittsburgh School of Medicine, under auspices of the Council on Clinical Cardiology of American Heart Assn., at St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Cont. Education, Mt. Zion Hospital & Medical Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

September 9-11—**Dermatology for the Family Physician and Internist.** Memorial Hospital Medical Center of Long Beach at Del Webb's Newporter Inn, Newport Beach. Thursday-Saturday. 21 hrs. $150 for physicians; $100, residents and interns. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

September 12-16—**American Academy for Cerebral Palsy.** Century Plaza Hotel, Los Angeles. Sunday-Thursday. 18 hrs. $85. Contact: James Bryan, Exec. Sec., AACP, 1255 New Hampshire Ave. NW, Suite 1030, Washington, D.C. 20036. (202) 659-8251.

September 13-17—**Dermatology for Primary Care Physicians.** UCSF. Monday-Friday. $400. Intensive preceptorial course presenting practical management of skin diseases that constitute a large part of daily practice. Enrollment limited to 10 primary care providers.

September 15-17—**Clinical Allergy for the Office Practitioner—International Symposium.** PMC at Rickey's Hyatt House, Palo Alto. Wednesday-Friday. $25.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. 11½ hrs. Contact: Ann Raisbeck, Dept. of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

September 18-19—**Practical Gastroenterology for the Family Physician.** UCLA. Saturday-Sunday.

September 21—**Lyman A. Brewer, III, Cardiothoracic Symposium—2nd Annual.** White Memorial Medical Center at Hilton Hotel, Los Angeles. Tuesday. Contact: Howard Whigham, White Memorial Medical Center, 1720 Brooklyn Ave., Los Angeles 90033. (213) 269-9131, ext. 429.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

September 25-October 1—**Cardiology 1976.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 29-30—**American Heart Association, Greater Los Angeles Affiliate—44th Annual Fall Symposium and 9th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday; 12 hrs. $60 for member of any heart assn.; $80, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 29-October 1—**San Francisco Heart Association—46th Annual Symposium.** Masonic Auditorium, San Francisco. Wednesday-Friday. Contact: S.F. Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 1-2—**Clinical Allergy.** Children's Hospital Medical Center, Oakland, at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Carty Calori, Med. Staff Admin. Asst., Children's Hospital Medical Center, 51st and Dover Sts., Oakland 94609. (415) 654-5600.

October 2-3—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 8-9—**Techniques for Dermatologic Research in the Office.** UCSF. Friday-Saturday.

October 12-14—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Golden Gateway Holiday Inn, San Francisco. Tuesday-Thursday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

October 14-17—**California Society of Internal Medicine—Annual Meeting.** Del Monte Hyatt, Monterey. Thursday-Sunday. Contact: Carol Holland Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 16-17—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 18-22—**Workshops in Internal Medicine.** American College of Physicians at University of Hawaii, Honolulu. Monday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, Pa. 19104.

October 30-November 6—**Evaluation of Neoplastic Lymphatic Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

November 3—**Echocardiography.** LLU. Wednesday. 6 hrs.

November 6-7—**Dermatologic Surgery—Skin Grafting.** See Surgery, November 6-7.

November 8-12—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 10—**Hypertension.** UCSF at Hyatt on Union Square, San Francisco. Wednesday.

November 13-14—**Kidney Function.** UCSF. Saturday-Sunday.

November 27-29—**Advances in Heart Disease—1977.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 8-10—**Respiratory Failure Workshop.** USC at Canyon Hotel, Palm Springs. Wednesday-Friday.

December 11—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. $250.

MENTAL RETARDATION

November 3-5—**Current Aspects of Mental Retardation.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

OBSTETRICS AND GYNECOLOGY

September 9-12—**Neonatology.** UCSD at Town and Country Convention Center, San Diego. Thursday-Sunday. Contact: Louis Gluck, MD, C-019 Biology Bldg., UCSD. (714) 452-4424.

September 13-15—**Medical Complications in Obstetrics and Gynecology—Annual Fall Symposium.** UCSF at Hyatt on Union Square, San Francisco. Monday-Wednesday.

September 15-22—**Workshops in (1) High Risk Pregnancy and (2) Infertility.** UCSF at Royal Lahaina Hotel, Maui, Hawaii. One week.

October 1-3—**Symposium on Perinatal Medicine.** National Foundation/March of Dimes; Long Beach and Orange County Obstetrics-Gynecology Societies; UCI at Memorial Hospital Medical Center, Long Beach. Friday-Sunday. $150. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3823.

October 2—**Endometriosis: Current Principles and Management—16th Annual Fall Seminar in Obstetrics and Gynecology.** Shufelt Society of Santa Clara Valley at Le Baron Hotel, San Jose. Saturday. 7 hrs. Contact: Vincent F. Nola, MD, Sect., Shufelt Society, 2081 Forest Ave., San Jose 95128.

October 5-8—**Fetal Monitoring.** USC. Tuesday-Friday.

October 6-8—**Recent Trends in Ob-Gyn.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

October 8-9—**Office Gynecology.** PMC at Hyatt on Union Square, San Francisco. Friday-Saturday. $90.

October 23—**Symposium on Endometrial Carcinoma.** See Cancer, October 23.

October 25-26—**New Horizons in Perinatal Intensive Care—5th Annual Seminar.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. Contact: Robin J. Grant, MPH, Coord. of Cont. Ed., Harbor General Hospital, 1124 W. Carson, Torrance 90502. (213) 328-2380, ext. 1374.

October 25-29—**Ob/Gyn Review.** USC at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

October 29—**Advances in Obstetrics and Gynecology.** UCD and Northern California Ob-Gyn Society at Red Lion Motor Inn, Sacramento. Friday. Contact: UCD.

PEDIATRICS

September 12-16—**American Academy for Cerebral Palsy.** See Of Interest to All, September 12-16.

October 22-23—**Nutrition in Children.** UCD and Sacramento Pediatric Society at Red Lion Motor Inn, Sacramento. Friday-Saturday. $45.

November 8-12—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 8-12.

December 4—**American Academy of Pediatrics, California Chapter I, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

PSYCHIATRY

September 15—**Office Psychiatry.** LLU. Wednesday. 6 hrs.

October 9—**Psychological Management of Chronic Pain.** UCLA. Saturday. 6½ hrs. $95.

November 8-12—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

December 2-5—**Treatment of Sexual Dysfunctions.** See Of Interest To All, December 2-5.

RADIOLOGY AND PATHOLOGY

September 18—**Radiology Symposium.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 1-3—**Society of Nuclear Medicine—1st Annual Western Regional Meeting.** Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Justine J. Lynch, Exec. Sec., No. and So. Calif. and Pacific NW Chapters, SNM, P.O. Box 40279, San Francisco 94140.

October 2—**Speech Pathology. USC.** Saturday.

October 15-17—**Radiology of the Genitourinary System.** American College of Radiology at Fairmont Hotel, San Francisco. Friday-Sunday. 15 hrs. $200 for members; $240, nonmembers. Contact: Maurine H. Trautz, Conf. Coord., ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015. (301) 654-6900.

October 21-29—**American Society of Clinical Pathologists and College of American Pathologists.** Hilton Hotel, Los Angeles.

Nine days. Contact: D. L. Gilcrest, ASCP, 2100 W. Harrison St., Chicago 60612.

October 26-29—**Symposium in Diagnostic Radiology.** UCSD at Vacation Village, San Diego. Tuesday-Friday.

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** See Cancer, December 12.

SURGERY AND ANESTHESIOLOGY

August 15-18—**Urology.** UCLA at Lake Arrowhead. Sunday-Wednesday.

September 10-11—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

September 11-18—**Practical Management of Anesthetic Problems—2nd Annual Symposium.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 12-16—**American Academy for Cerebral Palsy.** See Of Interest to All, September 12-16.

September 15-16—**Strabismus.** PMC at Stanford Court Hotel, San Francisco. Wednesday-Thursday. $175.

September 16-17—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 9-13—**American Society of Anesthesiologists—Annual Meeting.** Hilton Hotel, San Francisco. Saturday-Wednesday. 45 hrs. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

October 10-22—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 11-12—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Monday-Tuesday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

October 14-15—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 26-November 30—**Surgical Anatomy and Surgery.** USC. Tuesday evenings.

November 5-6—**Clinical Electromyography.** American Association of Electromyography and Electrodiagnosis at Sheraton-Harbor Island, San Diego. Friday-Saturday. 12 hrs. $100. Contact: W. C. Wiederholt, MD, 7010 Via Valverde, La Jolla 92037. (714) 459-8443.

November 6—**Bilateral Cleft Lip and Palate—Problems of Diagnosis and Treatment—8th Annual Symposium.** St. John's Hospital and Health Center, Santa Monica. Saturday. Contact: Cleft Palate Service, St. John's Hosp. and Health Ctr., 1328 22nd St., Santa Monica 90404. (213) 829-5511, ext. 2745.

November 6-7—**Dermatologic Surgery—Skin Grafting.** UCSF. Saturday-Sunday.

November 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 13—**Flexible Bronchofibroscopy Workshop.** PMC. Saturday. $250.

November 27-28—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Saturday-Sunday. $300; $150 for residents.

December 2-3—**Medical and Surgical Complications of Uveitis.** UCSF. Thursday-Friday.

December 3-4—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hosp. Med. Ctr., 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

December 3-5—**Electronystagmography Workshop.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

December 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

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OF INTEREST TO ALL PHYSICIANS

August 18-22—**Family Practice Refresher Course—3rd Annual.** UCLA. Wednesday-Sunday.

August 20-22—**Sexualis Traumaticus.** UCSD. Friday-Sunday.

August 22-27—**Family Practice Refresher Course.** UCD at Del Monte Hyatt, Monterey. Sunday-Friday.

August 23-27—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD. Monday-Friday.

August 28-September 4—**Family Practice Refresher Course—7th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $225. Contact: J. Blair Pace, MD, 101 City Dr. So., Orange 92668. (714) 634-5171.

August 29-September 2—**Autogenic Training.** UCLA at Asilomar. Sunday-Thursday.

August 29-September 6—**Pharmacology.** UCSF at Maui, Hawaii. Nine days.

August 31-October 19—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 9-11—**Dermatology for the Family Physician and Internist.** See Medicine, September 9-11.

September 12-16—**American Academy for Cerebral Palsy.** Century Plaza Hotel, Los Angeles. Sunday-Thursday. 18 hrs. $85. Contact: James Bryan, Exec. Sec., AACP, 1255 New Hampshire Ave. NW, Suite 1030, Washington, D.C. 20036. (202) 659-8251.

September 13-17—**Dermatology for Primary Care Physicians.** See Medicine, September 13-17.

September 15—**Office Psychiatry.** See Psychiatry, September 15.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** See Medicine, September 17-18.

September 18-19—**Practical Gastroenterology for the Family Physician.** See Medicine, September 18-19.

September 20-24—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

September 20-24—**Topics in Emergency Medicine—Basic Course.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

September 25-26—**The All-American Bicentennial Medicine Show.** UC Extension, Santa Cruz; Gladman Memorial Hospital, Oakland, at UC, Santa Cruz. Saturday-Sunday. 10 hrs. $50. Contact: Univ. of Calif. Extension, Santa Cruz 95064. (408) 429-2461.

September 28-December 12—**Bedside Clinics.** USC. Tuesdays.

October 7-9—**Western Occupational Health Conference—20th Annual.** Western Occupational Medical Association at Marriott Hotel, Los Angeles. Thursday-Saturday. Contact: Jack Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 9—**Psychological Management of Chronic Pain.** See Psychiatry, October 9.

October 11-15—**Primary Care.** STAN. Monday-Friday. $250.

October 21-22—**Old Age—Program on Geriatrics.** UCSF at Veteran's Home of California, Napa. Thursday-Friday.

October 24-27—**California Academy of Family Physicians.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: William R. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

October 25-29—**Family Practice Review.** LLU. Monday-Friday.

October 25-29—**Global Medicine and Diseases of Travel—120th Annual Scientific Meeting.** Hawaii Medical Association at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., HMA, 510 S. Beretania St., Room 201, Honolulu 96813. (808) 536-7702.

October 30-31—**Physiology of Respiration.** UCSF. Saturday-Sunday.

November 1-5—**Intensive Care.** STAN. Monday-Friday. $250.

November 1-5—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday.

November 5-6—**Clinical Electromyography.** See Surgery, November 5-6.

November 6—**Bilateral Cleft Lip and Palate—Problems of Diagnosis and Treatment.** See Surgery, November 6.

November 7-12—**American Academy of Physical Medicine and Rehabilitation.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: C. C. Herold, Exec. Dir., AAPMR, 30 N. Michigan Ave., Suite 900, Chicago, Ill. 60602.

November 11-12—**Emergency Medicine (Advanced Course).** UCSF. Thursday-Friday.

November 15-19—**Dermatology for Primary Care Physicians.** UCSF. Monday-Friday. $400. Intensive preceptorial course presenting practical management of skin diseases that constitute a large part of daily practice. Enrollment limited to 10 primary care providers.

November 19—**Diuretics.** USC. Friday.

December 1-3—**Immunizations—Review and Predictions.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

December 2-5—**Treatment of Sexual Dysfunctions.** USC at Canyon Hotel, Palm Springs. Thursday-Sunday.

December 9-11—**Genetics.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday.

December 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

SURGERY

September 6-7—**Western Orthopedic Society Annual Meeting.** Sunriver Lodge, Bend. Contact: Stanley E. Donahoo, MD, 1819 West Harvard Blvd., Roseburg 97470.

OF INTEREST TO ALL PHYSICIANS

September 18-19—**Advanced Life Support—Emergency Cardiac Care.** Providence Hospital, Portland. Contact: C. A. Hites, MD, 1500 S.W. 12th Avenue, Portland 97201.

September 22-24—**Oregon Medical Association Annual Scientific Session.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

October 1—**Oregon Gut Club Symposium.** University of Oregon Health Sciences Center, University Hospital South, 8B60, Portland. Contact: Clifford Melnyk, MD, Department of Gastroenterology, University of Oregon Health Sciences Center School of Medicine, 3181 S.W. Sam Jackson Park Road, Portland 97201.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

September 10-11—**University of Washington School of Medicine Alumni Days.** Friday-Saturday. Univ. of Wash. Sch. of Med., Seattle. Contact: William Bulger, Dir., Medical Alumni Assoc., HSB SC-60, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-3620.

September 10-13—**Washington State Medical Association Annual Meeting.** Friday-Monday. Olympic Hotel, Seattle. Contact: Harlan R. Knudson, Exec. Dir., 444 N.E. Ravenna Blvd., Seattle 98115. (206) 523-9110 or 1-800-552-0602.

September 13-17—**University of Washington School of Medicine Montana Circuit Course on Cancer.** Kalispell, Havre, Butte, Miles City. Dates and fee to be determined. Contact: Sidney Pratt, MD, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1491.

September 17—**Practical Aspects of Clinical Anaerobic Microbiology.** Friday. Registration: T-435 Health Sciences Building, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

September 23-24—**Ophthalmology and Otolaryngology for Primary Physicians.** Thursday-Friday. Registration: T-639 Health Sciences Building, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Div. of CME, HSC SC-50, Univ. of Wash. Sch of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 1-2—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 6—**Internal Medicine Review Sessions.** Wednesday evenings to June 1. T-625 Health Sciences Building, Univ. of Wash. Sch. of Med., Seattle. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 6-8—**Clinical Topics in Chest Disease.** (ACP). Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 19½ hrs. Fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 7-8—**Hospital and Health Facilities Infectious Disease Control.** Thursday-Friday. Health Sciences Building Auditorium, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 7-9—**Montana Medical Association Annual Meeting.** Thursday-Saturday. Heritage Inn, Great Falls, MT. Contact G. B. Zins, Exec. Dir., 2021 11th Ave., Helena, MT 59601.

October 7-9—**West Coast Allergy Society Annual Scientific Program.** Thursday-Saturday. Washington Plaza Hotel, Seattle. Contact: William H. Wilson, MD, Program Chairman, West Coast Allergy Society, 2164 S.W. Park Place, Portland, OR 97205. (503) 226-1555.

October 11-15—**University of Washington School of Medicine Eastern Washington Circuit Course on Pain.** 11, Moscow, ID; 12, Walla Walla; 13, Tri-Cities; 14, Yakima; 15, Wenatchee. Hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 15-17—**Western Dialysis and Transplant Society Annual Meeting.** Friday-Sunday. Olympic Hotel, Seattle. Physicians, $30; others, $20. Contact: Linda J. Huprich, Convention Mgr., 11633 Ventura Blvd., Encino, CA. (213) 981-0554.

October 22-23—**Aging and the Elderly.** Friday-Saturday. Seattle. Location, hours and fee to be determined. Contact: Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 22-23—**Sports Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

(Continued from Page 23)

OB-GYN—The Fresno County Department of Health is looking for a person interested in Family Planning and Antenatal Clinics in rural areas. These clinics are tied into a Regional Perinatal Center and Department's Decentralization Program. Public Health interest, experience, training desirable. California license required. Spanish fluency valuable. County pays malpractice insurance and contract range is $39,000 to $43,000. Write Donald T. Rice, MD, P.O. Box 11867, Fresno, CA 93775 or call (209) 488-3953.

UCLA SCHOOL OF MEDICINE, DEPARTMENT OF ANESTHESIOLOGY, seeks a Chairman of the Department of Anesthesiology at Kern Medical Center, its affiliate in Bakersfield, California. Board certification and California license essential. Salary open, full medical liability coverage. Interested candidates should direct inquiries or submit credentials (including curriculum vitae) to Donald F. Brayton, MD, Medical Director, Kern Medical Center, 1830 Flower Street, Bakersfield, California 93305; telephone (805) 322-3313. Both the University of California and Kern Medical Center are equal opportunity employers.

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HEMATOLOGIST AND MEDICAL ONCOLOGIST—33, AOA, triple board certified, university trained. Seeks opportunity for stimulating practice in specialty. Faculty position or group practice with academic affiliation preferred. Box 9475, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICING INTERNIST (Clinical Professor of Medicine) wishes employment during January, February, March preferably in Los Angeles South Bay. Special interests are Thyroid, Diabetes and Executive Type examinations. Write: Box 9474, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DERMATOLOGIST, board eligible, seeking group or solo practice with research affiliation. Prefer Pacific Northwest or Great Lakes areas. Available July '77. Please inquire re curriculum vitae and references to Box No. 9476, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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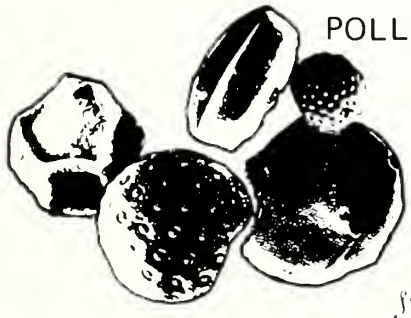

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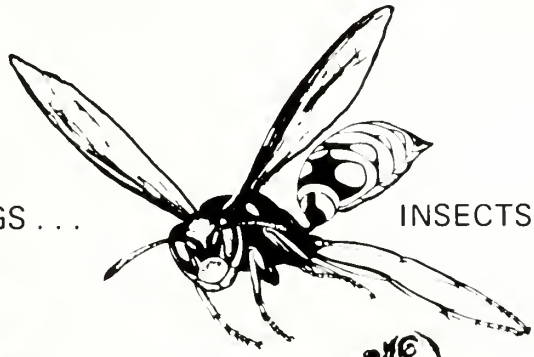

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REFERENCES

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Lancet 2:1105, 1967

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An In Vitro Test as used in the detection of immediate hypersensitivity in man.
V Latin American Congress of Allergy and Immunology National Academy of Medicine
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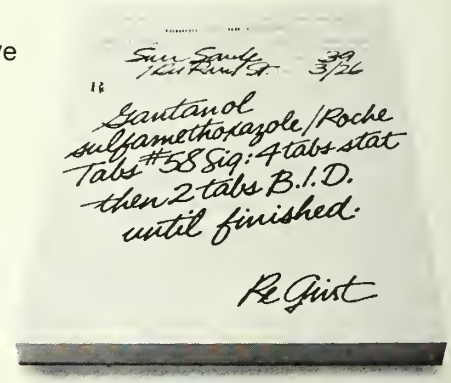

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Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

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The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

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New from
Lilly/Dista Research

NALFON®
fenoprofen calcium

A new
nonsteroidal agent
for relief of the
signs and symptoms
of rheumatoid
arthritis

See following pages for prescribing information.

NALFON
fenoprofen calcium

...reduces the pain and inflammation of rheumatoid arthritis* ...and it is well tolerated

New propionic acid derivative

NALFON (fenoprofen calcium)
300-mg.† Pulvules®

- Relieves arthritic pain
- Reduces inflammation
- Improves function and mobility
- Well tolerated
- Chemically unrelated to aspirin, indomethacin, phenylbutazone, or corticosteroids

600472

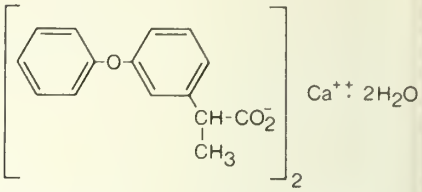
DISTA

*The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care).

†Present as 345.9 mg. of the calcium salt of fenoprofen dihydrate equivalent to 300 mg. fenoprofen

Description: Pulvules® Nalfon® (fenoprofen calcium, Dista) for oral administration contain fenoprofen calcium as the dihydrate in an amount equivalent to 300 mg. of fenoprofen. Nalfon is a nonsteroidal, anti-inflammatory drug. Chemically it is a propionic acid derivative.

The structural formula is as follows:



Calcium dl-2-(3-phenoxyphenyl) propionate dihydrate.

Nalfon is a white crystalline powder, soluble in U.S.P. ethanol (95%) to the extent of approximately 15 mg./ml. at 25 C°; slightly soluble in water, and insoluble in benzene.

The pKa of Nalfon is 4.5 at 25° C.

Clinical Pharmacology: Nalfon is a nonsteroidal, anti-inflammatory, anti-arthritic compound. In animal systems, it also shows analgesic and antipyretic activity. Its mode of action is unknown. In patients with rheumatoid arthritis, the anti-inflammatory action of Nalfon has been shown by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion. Its action is not mediated through the adrenal gland. There is no evidence that Nalfon alters the progressive course of the underlying disease.

To further demonstrate the anti-inflammatory activity of Nalfon in humans, the emergence and degree of erythemic response were measured in adult male volunteers exposed to ultraviolet irradiation. The effects of Nalfon, aspirin, and indomethacin were compared separately with those of placebo. All three drugs demonstrated anti-erythemic activity. The results in humans confirmed the anti-inflammatory activity found in animals.

Nalfon has been shown to inhibit prostaglandin synthetase isolated from bovine seminal vesicles. Reproduction studies in rats have shown Nalfon to be associated with prolonged labor and difficult parturition when given during late pregnancy. Evidence suggested that this may be due to decreased uterine contractility resulting from the inhibition of prostaglandin synthesis.

Under fasting conditions, Nalfon is rapidly absorbed, achieving peak plasma levels of 50 mcg. per ml. within two hours of oral administration of 600 mg. doses. Good dose proportionality was observed between 200 mg. and 600 mg. in fasting male volunteers. The plasma half-life is approximately 3 hours. Approximately 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4'-hydroxyfenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin.

The coadministration of aspirin decreases the biologic half-life of fenoprofen due to an increase in metabolic clearance which results in a greater amount of hydroxylated fenoprofen in the urine. Although the mechanism of interaction between fenoprofen and aspirin is not totally known, enzyme induction or displacement of fenoprofen from plasma albumin binding sites are possibilities. Chronic administration of phenobarbital, a known enzyme inducer, may be associated with a decrease in plasma half-life of fenoprofen. Clinical significance of these interactions is not known.

The concomitant administration of antacid (aluminum and magnesium hydroxide) does not interfere with absorption of Nalfon. Food ingestion decreases the rate and extent of absorption of Nalfon.

With single doses of Nalfon there is less suppression of collagen-induced platelet aggregation than with aspirin.

Fenoprofen shows anti-inflammatory effects in rodents by inhibiting the development of redness

and edema in acute inflammatory conditions and by reducing soft-tissue swelling and bone damage associated with chronic inflammation. It exhibits analgesic activity in rodents by inhibiting the writhing response in mice caused by the introduction of an irritant into the peritoneal cavity and by elevating pain thresholds to pressure in edematous hindpaws of rats. In rats made febrile by the subcutaneous administration of brewer's yeast, fenoprofen produces antipyretic action. These effects are characteristic of nonsteroidal, anti-inflammatory, antipyretic, analgesic drugs.

Indications and Usage: Nalfon® (fenoprofen calcium, Dista) is indicated for relief of the signs and symptoms of rheumatoid arthritis. It is indicated in the treatment of acute flares and in the long-term management of the disease. The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV. (Incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care.) Improvement in patients treated with Nalfon for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion.

In clinical studies in patients with rheumatoid arthritis, Nalfon has been shown to be comparable to aspirin in controlling the aforementioned measures of disease activity but the frequency of the milder gastrointestinal adverse effects (nausea, dyspepsia) and tinnitus was less than in aspirin-treated patients. It is not known whether Nalfon causes less peptic ulceration than aspirin.

In some patients Nalfon has been used in combination with gold salts or corticosteroids. Studies have been inadequate to demonstrate whether Nalfon adds any improvement in patients maintained on gold salts or corticosteroids. Whether Nalfon could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. The use of Nalfon in combination with salicylates is not recommended because there is no evidence to demonstrate that Nalfon would produce any additional effect beyond that produced by aspirin alone. Further, there is evidence that aspirin increases the rate of excretion of Nalfon.

There have been no studies in children; therefore the safety and effectiveness of Nalfon in children are unknown.

Contraindications: Nalfon is contraindicated in patients who have shown hypersensitivity to it.

Because the potential exists for cross sensitivity to aspirin and other nonsteroidal, anti-inflammatory drugs, Nalfon should not be given to patients in whom aspirin and other nonsteroidal, anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria.

Warnings: Nalfon should be given under close supervision to patients with a history of upper gastro-intestinal tract disease and only after consulting the "ADVERSE REACTIONS" section. Gastro-intestinal bleeding, sometimes severe, has been reported in patients receiving Nalfon.

In patients with active peptic ulcer and active rheumatoid arthritis, attempts should be made to treat the arthritis with nonulcerogenic drugs, such as gold. If Nalfon must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding.

In subacute and chronic studies in rats, Nalfon caused interstitial nephritis, glomerulonephritis and renal papillary necrosis. These abnormalities were dose-related and began to appear at doses approximating the human dose. In chronic studies in monkeys interstitial nephritis also occurred following Nalfon administration. Although this was seen at doses considerably above the human dose, lower doses were not studied in this species. During the course of the clinical trials one patient developed renal failure and died with a diagnosis of septicemia, bilateral suppurative pyelonephritis and renal papillary necrosis. It is not known whether these events were drug-related. A few patients developed mild elevations of the BUN during Nalfon® (fenoprofen calcium, Dista) therapy. Since Nalfon is eliminated primarily by the kidney, the drug should not be administered to patients with significantly impaired renal function. It is desirable to perform periodic renal function tests in all patients receiving Nalfon.

Precautions: In chronic studies in rats, high doses of Nalfon caused elevation of serum transaminase and hepatocellular hypertrophy. In clinical trials, some patients developed elevation of serum transaminase, LDH, and alkaline phosphatase which persisted for some months, and usually, but not always, declined despite continuation of the drug. The significance of this is unknown. It is recommended that periodic liver function tests be performed in patients receiving Nalfon and that the drug be discontinued if abnormalities occur.

The safety of this drug in pregnancy and lactation has not been established and its use during these events is, therefore, not recommended. Reproduction studies have been performed in rats and rabbits. When fenoprofen was given to rats during pregnancy and continued to the time of labor, parturition was prolonged. Similar results have been found with other nonsteroidal, anti-inflammatory drugs which inhibit prostaglandin synthetase.

In-vitro studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs which are also albumin bound and may lead to drug interaction. Theoretically, fenoprofen, as well as other nonsteroidal, anti-inflammatory agents, could likewise be displaced. Patients receiving hydantoin, sulfonamides, or sulfonylureas should be observed for signs of toxicity to these drugs. In patients receiving coumarin-type anticoagulants, the addition of Nalfon to therapy could prolong the prothrombin time. Patients receiving both drugs should be under careful observation.

In patients receiving concomitant Nalfon-steroid therapy, any reduction of steroid dose should be gradual to avoid the possible complications of sudden steroid withdrawal.

Patients with initial low hemoglobin values who are receiving long term Nalfon therapy should have a hemoglobin determination at reasonable intervals.

Peripheral edema has been observed in some patients taking Nalfon; therefore, Nalfon should be used with caution in patients with compromised cardiac function.

Studies to date have not shown changes in the eye attributed to Nalfon administration. However, because of adverse eye findings in animal studies with some other nonsteroidal anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after starting chronic Nalfon therapy and at periodic intervals thereafter.

Since food decreases Nalfon blood levels, the drug should be given 30 minutes before or two hours after meals during the daytime.

When phenobarbital, which may enhance the metabolism of Nalfon, is added or withdrawn, Nalfon dosage adjustment may be required.

Caution should be exercised by patients whose activities require alertness if they experience central nervous system side effects from Nalfon.

Since the safety of Nalfon in patients with impaired hearing loss has not been established, these patients should have periodic tests of auditory function when chronic Nalfon therapy is given.

Nalfon decreases platelet aggregation and prolongs bleeding time. Patients who may be adversely affected by prolongation of the bleeding time should be carefully observed when Nalfon is administered.

Adverse Reactions: *Digestive System*

The most common type of adverse reaction concerned the gastro-intestinal system. Dyspepsia occurred most frequently, being observed in about one out of seven patients. Other adverse reactions in descending order of frequency were: constipation, nausea, vomiting, abdominal pain, anorexia, occult blood in the stool, diarrhea, flatulence, and dry mouth.

Three instances of peptic ulceration and/or gastro-intestinal hemorrhage that may have been due to the drug and four instances in which drug relationship was questionable were observed in 3,391 individuals to whom the drug was administered for periods of time ranging up to 165 weeks.

In less than 2% of patients the drug was discontinued because of adverse gastro-intestinal reactions.

Skin and Appendages

The most common adverse effect was pruritus which was seen in about one out of ten patients. Other adverse reactions were: rash, increased sweating, and urticaria.

In about 1% of patients Nalfon® (fenoprofen calcium, Dista) was discontinued due to an adverse effect related to the skin.

Nervous System

The most frequent adverse reaction observed was somnolence which occurred in about one out of seven patients. Other adverse effects which occurred less frequently were: dizziness, tremor, confusion, and insomnia.

Nalfon was discontinued in less than 0.2% of patients because of these side effects.

Special Senses

The most common adverse reaction was tinnitus which was seen in about one out of ten patients. Other reactions observed in descending order of frequency were: blurred vision and decreased hearing.

In about 0.2% of patients Nalfon was discontinued due to adverse effects related to the special senses.

Cardiovascular

The most frequent adverse event observed was palpitations. This was noted in about one out of 25 patients. Tachycardia was observed less frequently.

In less than 0.5% of patients Nalfon was discontinued due to cardiovascular adverse reactions.

Laboratory

Anemia was noted in about one out of 500 patients. One patient required discontinuation of Nalfon therapy due to anemia. Increase in alkaline phosphatase, LDH, and SGOT were observed. ("See Precautions.")

Miscellaneous

Headache was seen in about one out of seven patients. Less frequently observed in descending order of frequency were: nervousness, asthenia, dyspnea, peripheral edema, fatigue, malaise, dysuria.

Overdosage: No specific information is available on the treatment of overdosage with Nalfon. If it should occur, standard procedures to evacuate gastric contents and to support vital functions should be employed. Since Nalfon is acidic and is excreted in the urine, it may be beneficial to administer alkali and induce diuresis. Furosemide (Lasix®) did not lower blood levels.

Dosage and Administration: For the initial treatment of rheumatoid arthritis, the recommended oral dose is 600 mg. four times a day. Although improvement may be seen in a few days in many patients, an additional two to three weeks may be required to gauge the full benefits of therapy. The dosage should be adjusted in accordance with the patient's condition and changes in disease activity. Daily dosage larger than 3200 mg. is not recommended. Nalfon should be administered 30 minutes before or at least two hours after meals. If gastro-intestinal complaints occur, administer Nalfon with meals or milk.

There have been no studies in children; therefore, the safety and effectiveness of Nalfon in children are unknown.

How Supplied: Pulvules Nalfon, 300 mg. (equivalent to fenoprofen), are supplied in bottles of 60 and 500 (No. 416). They are yellow and ocher in color. The Identi-Code® (formula identification code, Dista) symbol is H77.

DISTA 600472

Additional information available to the profession on request.

DISTA PRODUCTS COMPANY
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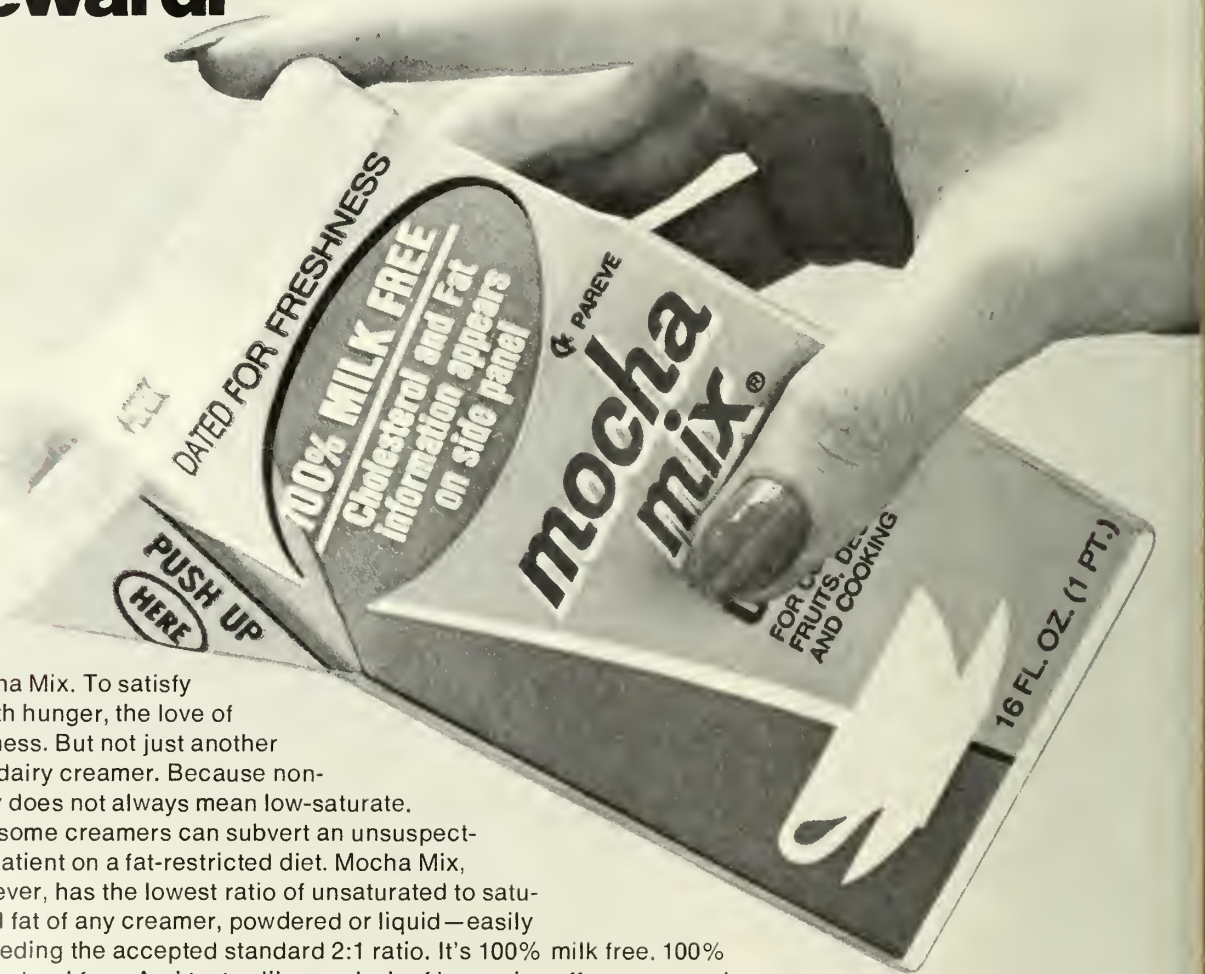
Indianapolis, Indiana 46206

What to do when your patient feels robbed of milk, cream and saturated fat.

Offer a reward.



Mocha Mix. To satisfy mouth hunger, the love of richness. But not just another non-dairy creamer. Because non-dairy does not always mean low-saturate. And some creamers can subvert an unsuspecting patient on a fat-restricted diet. Mocha Mix, however, has the lowest ratio of unsaturated to saturated fat of any creamer, powdered or liquid—easily exceeding the accepted standard 2:1 ratio. It's 100% milk free. 100% cholesterol free. And tastes like a splash of luxury in coffee, on cereal, fruit, dessert, even in cooking. If you must deprive your patient, add a reward for good behavior. Mocha Mix.

MOCHA MIX DATA SHEET

Portion Size 1 Fluid Ounce (2 Tbs.)

Servings per container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol	0

(Percentage of U.S. Recommended Daily Allowances (U.S., RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

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mocha mix® ...the non-dairy creamer that's lowest in saturated fat.

The anticholinergic action of Librax®*

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

Now available as a single entity

Quarzan®
(clidinium Br)

For potent antisecretory and antispasmodic action in adjunctive treatment of duodenal ulcer

ROCHE

Please see summary of product information on following page.

*Librax has been evaluated as possibly effective for its indications. (See brief summary.)

A therapeutic choice for effective antisecretory-antispasmodic action

Quarzan®
(clidinium Br)

2.5mg and 5mg capsules

Quarzan®
(clidinium Br)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Quarzan (clidinium Br) is effective as adjunctive therapy in peptic ulcer disease. **Anticholinergics have not been shown to be effective in contributing to the healing of peptic ulcer, decreasing the rate of recurrence or preventing complications.**
Contraindications: Known hypersensitivity to clidinium bromide or to other anticholinergic drugs, glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis.
Warnings: Anticholinergics may produce drowsiness or blurred vision; caution about activities requiring mental alertness. Heat prostration due to decreased sweating in high temperatures may occur. Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. Use of anticholinergics in patients with suspected intestinal obstruction would be inappropriate and possibly harmful. With overdosage, a curare-like action may occur.
Usage in Pregnancy and Nursing Mothers: Use of any drug in pregnancy or in women of childbearing potential requires that the potential benefit of the drug be weighed against the possible hazards to mother and fetus. As a general rule, anticholinergics should not be used by nursing mothers; their safety and efficacy in children has not been established.
Precautions: Exercise caution in elderly and in patients with autonomic neuropathy, hepatic or renal disease, ulcerative colitis, hyperthyroidism, cardiac conditions, hypertension, prostatic hypertrophy and hiatal hernia associated with reflux esophagitis.
Adverse Reactions: As with other anticholinergics, most frequently reported adverse effects are dryness of mouth, blurring of vision, urinary hesitancy and constipation. Other effects reported: decreased sweating, urinary retention, tachycardia, palpitations, dilation of the pupils, cycloplegia, increased ocular tension, loss of taste, headaches, nervousness, mental confusion, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, bloated feeling, impotence, suppression of lactation and severe allergic reactions including anaphylaxis, urticaria and other dermal manifestations.
Usual Daily Dosage: Individualize for maximum beneficial effects. Adults: 2.5 to 5 mg *t.i.d.* or *q.i.d.* a.c. and *h.s.* Geriatric or debilitated patients: 2.5 mg *t.i.d.* a.c. Desired pharmacological effect unlikely to be attained without occasional side effects.
Supplied: Quarzan (clidinium Br) capsules, 2.5 mg (green and red) and 5 mg (green and grey)—bottles of 100 and 500; Prescription Paks of 50, available singly and in trays of 10.

Librax®
Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide hydrochloride and/or clidinium bromide.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium® (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are avoidable in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of the mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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Division of Hoffmann-La Roche Inc.
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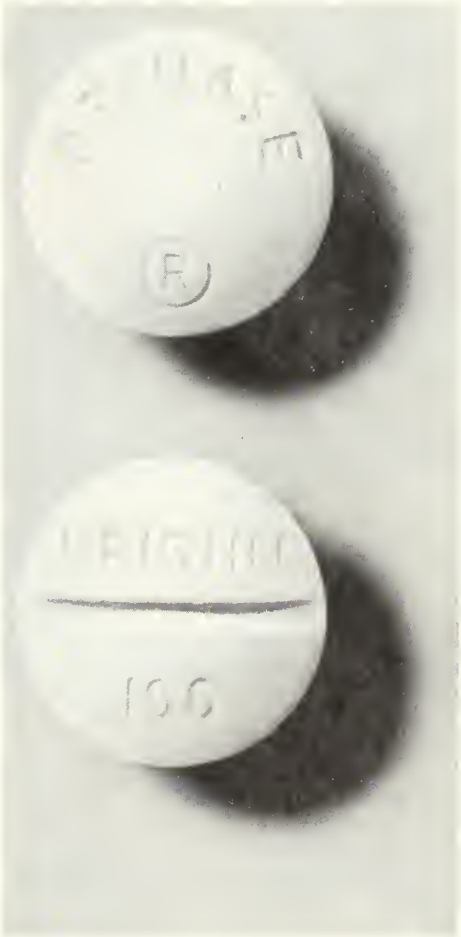

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You may wish to advise your patients that this change is taking place.

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In 3 double-blind, randomized, placebo-controlled studies[1-3] of patients with acute, painful musculoskeletal disorders affecting the back, Soma helped effect...

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for measurable relief

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Warnings: *Idiosyncratic Reactions* Rarely, extreme weakness, transient quadriplegia, dizziness, ataxia, temporary vision loss, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation have appeared within minutes or hours of the first dose. These usually subside in several hours but supportive and symptomatic therapy, including hospitalization, may be necessary.
Pregnancy and Lactation: Safe use not established; weigh potential benefits against potential hazards in pregnancy, nursing mothers (concentrations in breast milk are two to four times that in plasma), or women of childbearing potential.
Children Under Twelve Not recommended.
Potentially Hazardous Tasks: Driving a motor vehicle or operating machinery.
Additive Effects: Effects of carisoprodol and alcohol, other CNS depressants or psychotropic drugs may be additive.
Drug Dependence Use cautiously in addiction-prone patients.
Precautions: To avoid excess accumulation, use caution in patients with compromised liver or kidney function.
Adverse Reactions: *Central Nervous System.* Drowsiness, dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, idiosyncratic reaction (see "Warnings").
Allergic or Idiosyncratic In previously unexposed patients, these are usually seen after 1-4 doses and include rash, erythema multiforme, pruritus, eosinophilia, fixed drug eruption with cross reaction to meprobamate. Asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock may be manifestations of severe reactions. In such cases, stop carisoprodol and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids).
Cardiovascular Tachycardia, postural hypotension, facial flushing.
Gastrointestinal Nausea, vomiting, hiccup, epigastric distress.
Hematologic Leukopenia and pancytopenia (on carisoprodol plus other drugs).
Usual Adult Dosage: One 350 mg tablet three times daily and at bedtime.
Overdosage: Has produced stupor, coma, shock, respiratory depression, and, very rarely, death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, treat symptomatically; cautiously give respiratory assistance, CNS stimulants, pressor agents as needed. Carisoprodol is metabolized in the liver and excreted by the kidney. Diuresis and dialysis have been used successfully with related drug meprobamate. Carefully monitor urinary output; avoid overhydration; observe for possible relapse due to incomplete gastric emptying and delayed absorption.

Before prescribing, consult package circular or latest PDR information.

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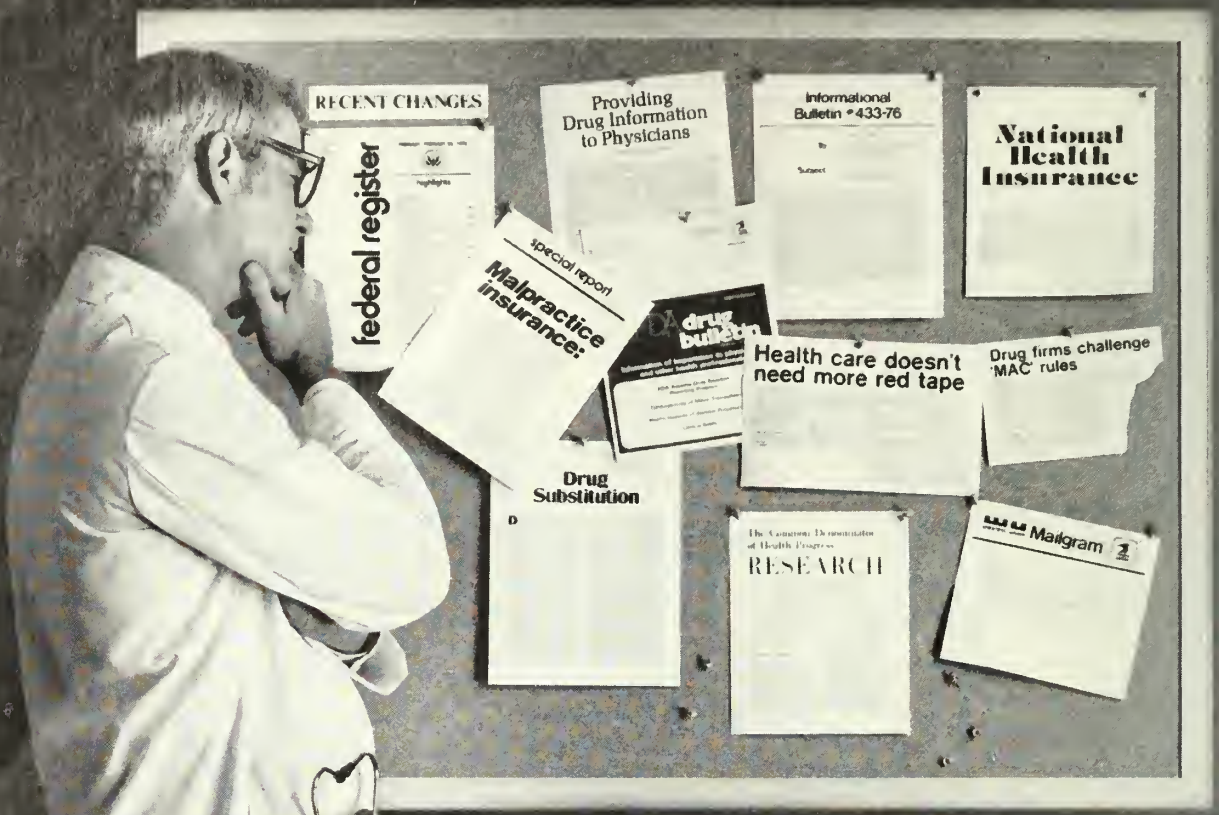
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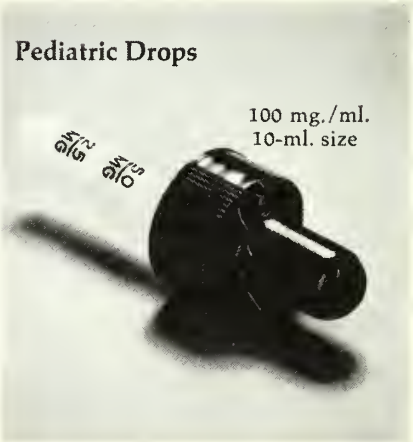

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Role of Platelets in Hemostasis and Thrombosis

ROBERT RODVIEN, MD *and* C. HAROLD MIELKE, JR., MD, *San Francisco*

Platelets interact with the coagulation factors in a complex way to arrest bleeding or generate thrombi. Recently, the platelet's relationship to endothelial alteration and atheroma production has received renewed attention. At present, tests of platelet function better define "hypocoagulable" rather than "hypercoagulable" states.

Hemostasis

UNDER NORMAL CONDITIONS (Figure 1), whenever a blood vessel is severed, several responses occur to staunch the flow of blood. If the vessel has a muscular coat, vascoconstriction occurs. In all vessels, the interface between vessel and blood is altered, promoting platelet adhesion to newly exposed subintimal structures. These adherent platelets release adenosine diphosphate (ADP) and cause other platelets to release more ADP, to form aggregates and ultimately to form a platelet plug. Platelet membrane phospholipid becomes available along with trace amounts of thrombin generated via the extrinsic pathway. The phospholipid and thrombin intensify the production of more thrombin[1,2] which began when the subintimal structures activated the contact factors—factors XII and XI. Thrombin is independently a strong inducer of platelet aggregation and simultaneously leads to fibrin formation with enlargement and impermeability of the platelet plug (Figure 2). Reduced blood flow and more thrombin production promote more fibrin deposition within minutes of the event. In time, white cells invade the thrombus.[3] Later, thrombus dissolution occurs as plasminogen, initially absorbed from the plasma and trapped within the thrombus, is altered to plasmin.[4] Completion of the healing process, when it occurs, involves recanalization and reconstitution of the endothelium. The recreated vessel may be normal, or there may be persistent abnormalities in the vessel wall with alterations in blood flow.

Therefore, hemostasis is the process that maintains the blood within the blood vessels. It is a complicated but efficient mechanism interlocking responses of the blood vessels, the platelets, the coagulation factors and the fibrinolytic mechanism.

Platelets: History

Platelets, a tenth the size of red cells, were discovered in the middle of the 19th century when a microscope with sufficient power became avail-

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ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
AMP = adenosine monophosphate
ASA = acetylsalicylic acid
ATP = adenosine triphosphate
LASS = labile aggregation stimulating substance
MDA = malonyldialdehyde
PG = prostaglandin

able. A major conflict developed: Were the platelets artifacts, white cell granules, or the precursors to either the white cell or the red cell? Almost no one associated platelets with fibrin formation.

In 1882 the experiments of Bizzozero of Turin[5] showed that the initial stages of thrombosis involved platelets. Still, by the turn of the century many investigators felt platelets were either artifacts or at best of minimal importance. Platelets were still cells in search of a function.

In 1905 Pratt[6] developed the first method to count platelets and in 1910 Duke[7] added the "bleeding time." Eventually, modifications of this method would be used to differentiate between qualitative and quantitative defects in platelets. The next major advance occurred when electron microscopy was used to examine platelet morphology.

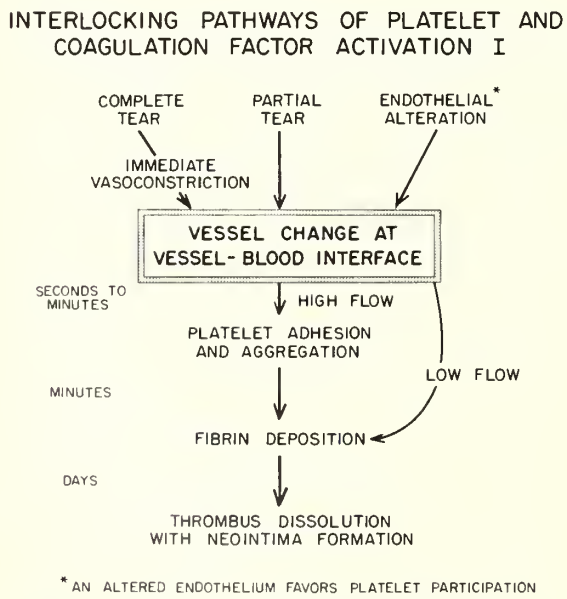

Figure 1.—Shown is a schematic representation of the normal response of blood to changes in the vessel wall. The effects of disordered flow as well as the interactions of the platelets and coagulation factors have been omitted (see Figure 2). These reactions may be inappropriately triggered by endothelial cell changes or abnormal flow leading to thrombosis rather than hemostasis. These stimuli that lead to thrombosis probably favor greater platelet participation in the process.

In 1960 Gaarder and co-workers[8] showed that adenosine diphosphate aggregates platelets suspended in plasma. With the development of platelet aggregometry by Born in 1962,[9] an explosion in platelet research occurred to form our present-day understanding of the platelet functions in hemostasis and thrombosis.

Platelets: Their First Function

Platelets respond to a variety of substances by altering their shape, adhering to the material to which they are exposed, changing their ectomembrane constituents and undergoing the "release reaction." Substances shown to produce this reaction include materials as diverse as proteolytic and structural proteins (such as thrombin and collagen), vasoactive materials (such as serotonin and epinephrine), nucleotides (such as ADP), polypeptide hormones (such as vasopressin) and nonbiologic surfaces (such as glass, latex particles

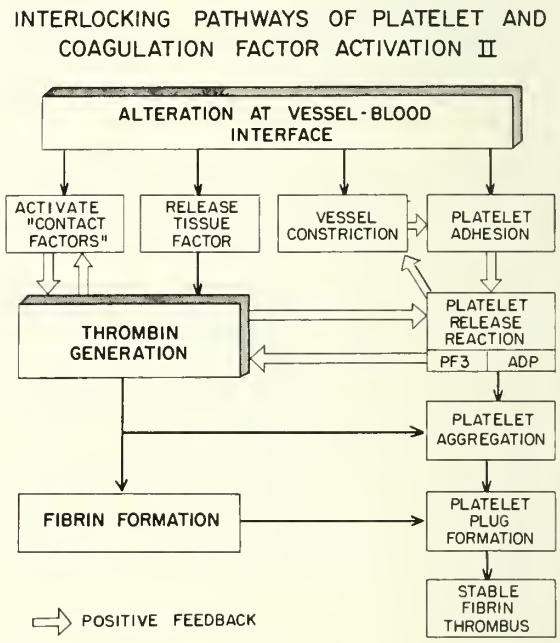

Figure 2.—The production of thrombin in response to vessel wall changes is begun by activation of the coagulation factors and release of tissue factor, and amplified by the presence of the platelet surface and autocatalytic mechanisms. Similarly, platelet recruitment to form a plug has a "positive feedback" quality because the release of stored adenosine diphosphate (ADP) promotes further release of ADP. Therefore, prevention of these reactions is most effective when the vessel wall alteration is prevented. Once these interlocking reactions are initiated, the process can only be blunted. Acetylsalicylic acid acts to prevent the release of ADP from the platelet; it does not affect thrombin generation or the other platelet reactions. PF3 indicates platelet factor 3.

and polyvinyl chloride).[10] The release reaction involves an explosive movement of intracellular granules to the center of the platelet. Degranulation releases cations, vasoactive amines, proteins, nucleotides and other materials into the plasma via an intricate canulicular system.

The release reaction has been divided into two types according to the agonist that produces the reaction. Type I agonists—ADP, epinephrine and collagen—release a number of constituents; for example, nonmetabolic adenosine triphosphate (ATP) and ADP, serotonin, calcium and platelet factor 4 (PF4). The stronger type II agonists (of which thrombin is the only physiologic agent) release additional constituents: for example, fibrinogen and lysosomal enzymes.[10]

Evidence is accumulating that underlying the response to these various stimuli there is a basic mechanism involving all three second messenger systems: the obligate intermediates of prostaglandin (PG) synthesis, calcium ions, and cyclic adenosine monophosphate (AMP).[11] A reasonable hypothesis (Figure 3) presently being tested in several laboratories is that platelet agonists interact with specific receptor sites on the membrane, activating phospholipase A_2.[12] Arachidonic acid,

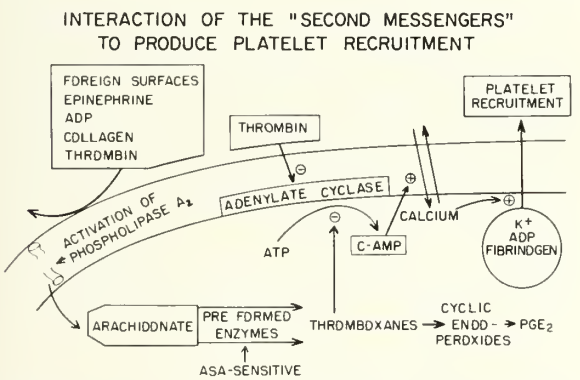

Figure 3.—Platelets are responsive to a number of different stimuli, and in turn respond in a relatively uniform fashion by serially (1) activating membrane phospholipase, (2) releasing arachadonate into the cytoplasm, (3) producing prostaglandins (PG), (4) depressing adenylate cyclase activity, (5) diminishing a pool(s) of cyclic adenosine monophosphate (C-AMP), (6) promoting greater entrance of calcium into the cell and (7) releasing preformed packets and other cytoplasmic constituents into the extracellular space. The materials released include adenosine diphosphate (ADP) which promotes platelet recruitment into the platelet plug. Acetylsalicylic acid (ASA) prevents the formation of the intermediates of PG (labeled "thromboxanes") and therefore diminishes the extent of the "release reaction" by this mechanism. Thrombin may act at multiple sites including a site distant to the ASA-induced change to allow platelets to participate in hemostasis. ATP indicates adenosine diphosphate.

which exists in large quantities in the platelet and specifically as part of the membrane phospholipids,[13] is released into the cytoplasm by this enzyme. There this fatty acid is transformed by one of two parallel preexistent enzyme systems into the prostaglandins E_2 and $F_{2\text{-alpha}}$ (PGE_2 and $PGF_{2\text{-alpha}}$) with the formation of very important intermediates. These intermediates—an endoperoxide (labile aggregation stimulating substance, LASS), cyclic ethers (thromboxames) and other PG's—may have ancillary functions; for example, vasoconstriction.[14-17] Presumably one of these intermediates is the common denominator producing the same or a similar "release reaction" in response to all or many of the various platelet agonists. The prostaglandins E_2 and $F_{2\text{-alpha}}$ are produced in relatively small amounts by these transformation pathways and functionally are not nearly as important as some of the more prevalent intermediates.

Collagen, thrombin and epinephrine have been shown to depress membrane adenylate cyclase activity and, therefore, platelet cyclic AMP pools, but the relationship of this biochemical event to platelet aggregation is unclear.[18] These two second messengers interact since increases in PGE_2 and $PGF_{2\text{-alpha}}$ production depress adenylate cyclase activity.[19] Calcium—another second messenger in many cells—is also important for platelet reactivity. Translocation of calcium between intracellular pools is crucial to the "release reaction."[20,21] How the three "second messengers"—PG's, cyclic nucleotides and divalent cations—interact to presumably produce adhesion, release, aggregation and the eventual promotion of a gelatinous thrombus by fibrin production is still not completely clear. Partial blockade of this subcellular mechanism still may not prevent platelet participation in hemostasis. The effect of acetylsalicylic acid (ASA) on platelets is an example of partial blockade. ASA and severe thrombocytopenia do not produce equivalent degrees of bleeding or prolongation of the template bleeding time. Platelets exposed to ASA can participate in plug formation[22] and therefore in hemostasis.

The mechanism by which a thrombus stops propagating is not immediately obvious. Thrombin is autocatalytic to its own production,[23] and is produced in increasing amounts in the microenvironment of adherent, activated platelets.[24,25] Similarly, activation of platelets is promoted by thrombin and leads to more platelet activation. Both these interlocking events—thrombin produc-

tion and platelet activation—are therefore positive feedback systems in contrast to the "negative feedback" mechanisms characteristic of hormonal regulation. Extension of the thrombus is regulated by flow—producing dilution of platelet aggregates and activated factors. In addition, thrombin produces competitive inhibitors of the coagulation cascade by proteolytic digestion of previously activated coagulation proteins.[25-27] These fragments also limit the size of the thrombus. The physiologic role of the antithrombins in modifying thrombus growth is unknown.

Hemostasis Versus Thrombosis

Thrombosis is not equivalent to hemostasis, but is a distortion of the hemostatic process. Both hemostasis and thrombosis involve the vessel wall, the fibrinolytic system, the coagulation factors and the platelets to produce an endovascular insoluble matrix of fibrin, erythrocytes and leukocytes. Both have common modifiers; for instance, the rate of blood flow. The relative participation of platelets and the soluble coagulation factors in the early interactions with the vessel wall is probably very dependent on the velocity and quality of blood flow. Rapid or disordered flow promotes vessel wall-platelet and platelet-platelet interaction; slow flow may lead to a thrombus composed primarily of fibrin. Some of the differences between thrombosis and hemostasis are now evident. The trigger to hemostasis is a change in the vessel wall and the primary platelet agonist may be extravascular collagen. However, thrombosis can occur because of a change in flow, a vessel wall abnormality or "hypercoagulability" of the blood. Platelets may react to another abnormality (the suspicion is that it may be intravascular thrombin or that they may themselves be the trigger to inappropriate thrombus formation). In the future, platelet-suppressive drugs may be able to control the thrombotic response without impairing hemostasis. In fact, there is circumstantial evidence to suggest that aspirin and other drugs may accomplish this task. Clinical trials are underway but, as yet, there is no definite evidence that platelet-active drugs are antithrombotic.

Partial blockade of platelet function may be an important phenomenon in clinical medicine. There is no doubt that ASA (as the best known example among numerous drugs) blunts the platelet's capacity to participate in hemostasis. It is not complete blockade; platelets affected by ASA still produce a platelet plug faster than diminished numbers of platelets or no platelets at all. There must be an alternative ASA-insensitive mechanism for the production of platelet aggregates. Thrombin-induced aggregation and release may be this mechanism. The best data to support this suggestion are the experiments of nature in man in which thrombin and fibrin formation are seriously impaired. When factor VIII and factor IX deficient subjects have been treated with ASA,[28] the bleeding time has been, in most instances, notably prolonged. In some of these persons, administration of the deficient soluble coagulation factor was necessary to stop bleeding at the bleeding time site. Fibrin deposition alone cannot be used to explain the prolongation of the bleeding time after ASA administration because this mechanism may be completely intact in people with afibrinoginemia.[29] Therefore, platelets must participate in the cessation of bleeding of a person who has ingested ASA. These findings, taken together, strongly suggest that thrombin or some other intermediate in the coagulation cascade can produce effective platelet function when acetylsalicylic acid has blunted platelet aggregation and release.

It is not clear at the present time what the physiologic mediators of *in vivo* platelet function are. Traditionally, ADP and collagen are considered to be important. However, the intravenous infusion of ADP does not lead to a retractable impermeable plug. ADP produces only reversible aggregates *in vivo*.[30] There is evidence from some reports to suggest that thrombin may be a major, if not the dominant, mediator of platelet adhesion, aggregation and release *in vivo*[31,32] although other reports disagree.[33] Thrombin may be capable of causing release of serotonin from platelets despite ASA's prevention of PG production as shown by Smith and Willis (Figure 3).[34] It has been known for some time that thrombin produces a more profound change in the platelets than most other platelet agonists.[35] There is some evidence to suggest that there are multiple receptor sites on platelet membranes for thrombin,[36] again suggesting alternative mechanisms of platelet activation, some of which may be ASA-sensitive and others of which may be ASA-insensitive. Thrombin's role may explain why ASA blunts but does not cripple hemostasis.

Platelets: Their Other Functions

This analysis of platelet function has emphasized its role to promote hemostasis and to partici-

pate in thrombogenesis. Other functions for platelets are also known:

- Platelets cause leukocytes to accumulate around the platelet plug; that is, they may release chemotactic substances.[37,38]
- Platelets do release vasoactive amines.[39]
- Platelets may release hydrolytic and proteolytic enzymes directly into the intimal and subintimal structures provoking changes that may eventually lead to atheroma.[40]
- Platelets act to transport serotonin from sites of synthesis (the gut) to other sites of function.

At least some of these functions relate to the two-edged sword of hemostasis-thrombosis.[41]

Tests of These Functions

Laboratory tests of platelet function have traditionally been designed to test platelet "hypofunction"; that is, inability to respond fully to a hemostatic challenge. These tests include the bleeding time,[42] platelet count, morphology, clot retraction, prothrombin consumption, adhesion, aggregation in response to a number of agonists and release of serotonin or platelet factor 3 (PF3). In addition, acid phosphatase can be used *in vitro* and platelet survival (using ^{51}Chromium[43] or malonyldialdehyde [MDA][44]) *in vivo* to assess platelet kinetics.

Recently, investigators have attempted once more to overcome their frustrations and test the role of platelets in mediating thrombotic diseases such as stroke, myocardial infarction and atherosclerosis. *In vivo* platelet survival is being reevaluated and other tests have been added. Some of these newer, less invasive, procedures attempt to evaluate platelet turnover by measuring platelet specific proteins that normally are not detected in cell free plasma. These tests include the platelet factor 4 analysis,[45] release of specific isoenzymes[49] and beta-thromboglobulin assay.[48] Platelet turnover may also be indirectly measured by platelet sizing[47] because platelets newly released from the marrow are bigger than the general population of platelets. Increased numbers of circulating aggregates[46] may also be markers for platelet-mediated thrombotic events.

Further Reading on Platelets

For detailed reviews about platelet physiology, pathophysiology and use of platelet-suppressive drugs, the reader is referred to the articles by Weiss,[50] by Genton and co-workers,[51] by Mustard and Packham[52] and by us.[53]

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Initial Care in the Immediate Postburn Period

The magnitude of the injury in a burn patient depends both on the depth of the burn and its extent. And as far as burn wound depth goes for hospital care, the important differentiation is between partial (or second degree) burn and third degree burn, in which all skin appendages have been destroyed and some grafting is required for definitive coverage. This is important in terms of function and of need for grafting. More important in the initial care is the extent of burn which can be most readily assessed, using the rule of 9's where various anatomical divisions of the body represent 9 percent or a multiple thereof (the upper limb is 9, lower limb is 18, anterior or posterior trunk 18 each, head and neck 9, perineum and genitalia 1).

In the initial care of a burn patient, one directs his attention to establishment of a secure intravenous pathway for the administration of resuscitation fluids; determination of the need for a tracheostomy (and that is seldom today); the need for an escharotomy . . . ; tetanus immunization (a booster if the patient has had prior active immunization; otherwise, begin active immunization and give hyperimmune tetanus antiserum). Now, in the only instance where wound care takes any precedence at all is in the case of patients with chemical injuries where the severity of the burn depends not only upon the concentration of the agent to which there has been exposure but also upon the duration of contact. And in patients with chemical burns, immediate dilution of the offending agent with copious water lavage should be carried out.

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Heparin Prophylaxis for Deep Vein Thrombosis and Pulmonary Embolism

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Thromboembolic prophylaxis remains a significant problem and is obviously incompletely understood. It would appear, however, that at present the information available implies several points. First, administration of low-dose heparin is efficacious in preventing deep vein thrombosis and pulmonary emboli in most general surgical patients who are at risk for thromboembolic complications. Second, low-dose heparin probably works by augmenting the effect of the naturally occurring inhibitor to Factor Xa. Third, patients in whom surgical operations are done and extensive tissue dissection or postoperative immobilization (such as hip arthroplasties) is required are probably not protected by low-dose heparin administration; full anticoagulation with warfarin or treatment with one of the platelet antiaggregating agents should be carried out. Fourth, any form of anticoagulation carries some risk of bleeding complications, but it appears that the incidence of major bleeding complications is not significantly greater in the treatment groups.

DEEP VEIN THROMBOSIS and thrombophlebitis are responsible for a significant degree of morbidity in hospital. The complications, particularly chronic venous insufficiency and pulmonary emboli, are also important medical problems; the former contributing heavily to chronic disability and the latter a leading cause of death. It is estimated that in the United States there are 182,000 new cases of thrombophlebitis and 106,000 cases of pulmonary emboli annually.[1] Therefore, thromboembolic complications occur in a little over a quarter of a million patients each year, many of these complications occurring while the patients are in the hospital. Hume and co-workers estimated that 5 of every 1,000 adults in whom major surgical procedures are carried out will die from a massive pulmonary embolus.[1] Because of the magnitude of this problem, a number of investigators have explored the possibility of using low-dose heparin or other forms of anticoagulation as prophylaxis against deep vein thrombosis and pulmonary emboli.

A great deal has been learned about the incidence of deep vein thrombosis since the develop-

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ment of accurate diagnostic techniques. The most widely used at this time is the ^{125}I-fibrinogen scan which utilizes radioactively labeled fibrinogen to detect venous thrombosis. Early work by Kakkar has shown that the actual incidence of deep vein thrombosis as detected by the ^{125}I-fibrinogen scan, is between 30 and 35 percent in patients in whom major surgical procedures are done.[2,3] In only about half of these will the classical physical findings of thrombophlebitis be seen. This work also showed that about half of all cases of deep vein thrombosis occur in the perioperative period. Many investigators have utilized the ^{125}I-fibrinogen scan, and it has subsequently been accepted as an accurate technique for the detection of deep vein thrombosis. Work by Harris and his colleagues showed that the results of fibrinogen scan correlated with those on phlebograms in 83 percent of the cases in which they were attempting to document fresh thrombi.[4]

It is recognized that certain patients are more prone to thromboembolic complications than others. Work by Kakkar and associates has defined this high risk group.[3] He studied 203 patients over the age of 40 who were admitted for elective surgical operations. In all patients studies were made utilizing the ^{125}I-fibrinogen scan. Certain patients were found to have an inordinately high incidence of deep vein thrombosis—such as patients with previous pulmonary emboli (100 percent), previous history of deep vein thrombosis (68.4 percent), varicose veins (56.5 percent), obesity (47.9 percent), malignancy (40.7 percent) and increased age (45.7 percent in patients over 60 years of age and 24.4 percent in patients under 60 years of age). This study therefore defined those patients in whom thromboembolic complications are most likely to occur and who would therefore be candidates for some form of prophylactic therapy.

The possible use of low-dose heparin was suggested 25 years ago by DeTakats when he noted that it took less heparin to prevent clotting than to stop it.[5] Kakkar and co-workers were the first

TABLE 1.—*Efficacy of Low-Dose Heparin Administration*

Author	*Date*	*Number of Patients*	*Regimen*	*Incidence of Deep Vein Thrombosis*		*Remarks*
				Control (percent)	*Low-Dose Heparin (percent)*	
Kakkar, Field, et al[6]	1971	53	5,000 units 2 hours before and 24 hours after surgical operation, then every 12 hours for 5 days	26.0	4.0	Patients over age 50 for elective hernia repair
Williams[7]	1971	56	10,000 units 10 hours preoperatively, 2,500-5,000 units every 6 hours for 7 days	41.0	15.0	Patients over age 50 for abdominal surgical procedures
Nicolaides, et al[8]	1972	251	5,000 units 2 hours before operation and then every 12 hours for 7 days	24.0	0.8	Patients over age 40 for major surgical operation
Kakkar, Corrigan, et al[9]	1972	78	5,000 units 2 hours before operation, then 5,000 units every 12 hours for 7 days	42.0	8.0	Double-blind study with patients over age 40
Gordon-Smith, et al[10]	1972	150	5,000 units 2 hours before operation, then 5,000 units every 12 hours for 7 days	42.0	13.5* 8.3†	Patients over age 40 in whom major surgical operation was done
Gallus, et al[11]	1973	226	5,000 units 2 hours before operation and then every 8 hours until ambulatory	16.0	2.0	Patients over age 40 in whom elective surgical operation was done
		46	5,000 units after admission and then 5,000 units every 8 hours through surgical operation	48.0	13.0	Patients admitted for emergency operation for hip fracture
Evarts and Alfidi[12]	1973	25	5,000 units 2 hours preoperatively and then 5,000 units every 12 hours for 7-10 days	..	28.0	Patients undergoing total hip replacement
Covey, et al[13]	1975	105	5,000 units preoperatively and then 5,000 units every 12 hours for 8 days	9.6	7.5	Patients over age 40 undergoing elective surgical operation, double-blind

*Heparin for 3 days †Heparin for 7 days

to utilize low-dose heparin in a clinical trial to test its efficacy in preventing venous thrombosis in surgical patients.[6] Since that time a number of other investigators have carried out clinical trials with low-dose heparin.[7-13] Although the protocol has varied among investigators the results have documented the efficacy of low-dose heparin administration in preventing deep vein thrombosis in postoperative patients (see Table 1).

Low-dose heparin is usually defined as 5,000 units administered subcutaneously 2 hours before surgical operation and then every 12 hours in the postoperative period for five to seven days or until the patient is fully ambulatory. However, some investigators have varied this protocol (see Table 1). The consensus from these studies is that low-dose heparin is effective in decreasing the incidence of deep vein thrombosis in patients in whom general, thoracic or gynecological surgical procedures are carried out. Patients in whom prostatectomy[7] or hip reconstruction procedures[12] are done were not protected. The low incidence of deep vein thrombosis in Covey's series is difficult to explain; the authors hypothesized that it might be due to the large number of patients taking aspirin or to the type of fibrinogen used to detect deep vein thrombosis.

The next obvious step was to determine whether decreasing the incidence of venous thrombosis had any effect on decreasing the occurrence of pulmonary embolism. Sagar and coworkers prospectively studied 500 patients in whom elective surgical operations were carried out and found no deaths attributable to pulmonary emboli among the 252 patients in whom low-dose heparin was administered, while eight of 236 patients (3.4 percent) of the control group died as a result of pulmonary emboli.[14] Results in a recently published international multicenter trial, coordinated by Kakkar and his colleagues, have provided definitive information about the role of low-dose heparin in preventing pulmonary emboli.[15] The cases of more than 4,000 patients were studied in this report. The heparin regimen was 5,000 units given subcutaneously two hours preoperatively and then every eight hours for seven days. Sixteen patients in the control group (0.77 percent) and two in the heparin-treated group (0.09 percent) died as a direct result of pulmonary emboli, a statistically significant difference. In the same study, deep vein thrombosis was detected in 24.6 percent of the control group and 7.7 percent of the heparin-treated group. In only five patients in the heparin group did the venous thrombosis extend above the knee, while this occurred in 49 patients of the control group. Findings in this study showed no statistically significant difference in the transfusion requirements or in postoperative hemoglobin drop between the control and the heparin-treated patients. However, the incidence of excessive intraoperative blood loss and wound hematomas was slightly greater in the heparin treated group. In only 53 of the 2,045 patients in the heparin group was discontinuation of heparin required because of bleeding complications.

One question naturally arises: Why does heparin, in what would normally be considered nonanticoagulating doses, have an antithrombotic effect? While the exact mechanism still remains to be explained, many theories have been offered. The most widely accepted has been that offered by Wessler and his colleagues.[16,17] They have suggested that the prevention of a hypercoagulable state is dependent upon the neutralization of activated Factor X (Xa), which is normally the result of a naturally occurring inhibitor to Xa. They have also suggested that small amounts of heparin will greatly increase the rate of Xa neutralization by its inhibitors—that is, augment severalfold the capacity of one's own naturally occurring inhibitors to block the activity of Xa and hence the conversion of prothrombin to thrombin.

Wessler and his colleagues have also shown that the inhibitor to Xa is one and the same as antithrombin III and heparin cofactor.[17] Reduction in antithrombin III levels may favor the development of postoperative thrombosis, and in patients in whom there is a decreased antithrombin III level there may be no response to low-dose heparin administration if the inhibitor system is significantly compromised.

In summary, it would appear that the coagulation cascade may be interrupted at the level of activated Factor X(Xa) by small amounts of heparin, providing the stimulus to coagulation is not so great that the amount of Factor X that is activated exceeds that which can be neutralized by heparin in conjunction with the naturally occurring Xa inhibitor and that Xa is neutralized before the actual formation of fibrin has begun (that is, administration of heparin is begun preoperatively). This would explain the failure of low-dose heparin administration to be effective in patients, such as those with hip fractures or hip reconstructions, in whom there is major tissue

dissection as part of the operative procedure. In these cases the stimulus for clotting overrides the protective effect of low-dose heparin.

Other drugs, primarily warfarin and platelet antiaggregating agents, have also been studied for their usefulness in preventing thromboembolic complications. Sevitt and Gallagher were the first to investigate the efficacy of an oral anticoagulant of the warfarin type (phenindione).[18] They studied the cases of patients over the age of 55 with hip fractures and found a 28.7 percent incidence of thrombophlebitis in the control group and a 2.7 percent incidence in the phenindione series. There were 15 deaths from pulmonary emboli in the control group and only two deaths in the anticoagulated group, both of which occurred after therapy had been discontinued.

Salzman and associates also studied the value of prophylactic anticoagulation with warfarin in patients with hip fractures.[19] They noted a 7 percent incidence of pulmonary embolism in the control group while in none of the patients in the anticoagulated group was an embolism present. Thrombophlebitis, detected clinically, occurred in 22 percent of the control patients and 7 percent of the warfarin group. Findings in a similar study using warfarin prophylaxis in patients in whom hip arthroplasties were done at the Massachusetts General Hospital showed a 36 percent incidence of thromboembolic complications in the control group as opposed to 9 percent in the warfarin group.[20] There were seven (10 percent) cases of pulmonary embolism in the control group while there were no pulmonary emboli in the treated group. In all of the above studies, full anticoagulation was the goal.

Whenever full anticoagulation, as opposed to low-dose heparin administration, is utilized, a higher incidence of bleeding complications would be anticipated. In Salzman's series the incidence of major bleeding in the treated group was 7 per cent, and 5 percent in the control group.[19] Harris noted an increase in local and distant bleeding complications where warfarin was used in elective surgical procedures on the hip.[20] For example, wound hematomas occurred in 23 percent of the warfarin group and 18 percent of the control group. However, their differences appear to be small and actual cessation of anticoagulation was required in only two cases because of persistent bleeding and no patient had a prolonged stay in hospital because of anticoagulation.

Salzman and his group have also studied the efficacy of agents which effect platelet function—dipyridamole, aspirin and dextran.[21] They found no protection from dipyridamole, though aspirin and dextran both proved as effective as warfarin in preventing thromboembolic complications. The incidence of major bleeding complications did not differ significantly among the groups treated with warfarin, aspirin, dipyridamole and dextran. However, in the group receiving aspirin a significantly greater volume of postoperative transfusion was required and only in the warfarin group did bleeding lead to a discontinuation of therapy (four patients). However, results of a similar study, from Stinchfield's service in New York, failed to show any protective effect from administration of dextran.

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Outpatient Heroin Detoxification with Acupuncture and Staplepuncture

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Eighteen heroin addicts were treated as outpatients with acupuncture, electrical stimulation and staplepuncture. Results of treatment were compared with results in two similar groups of 18 persons in whom detoxification was carried out using methadone and propoxyphene napsylate. Withdrawal symptoms were relieved for about two hours in most of the patients after a treatment episode of acupuncture and electrical stimulation. Staplepuncture, which is the manipulation by hand of a surgical staple implanted in the concha of the ear, was reported to relieve withdrawal symptoms at least partially in approximately 40 percent of subjects. In only one person of the group treated with acupuncture or staplepuncture was complete detoxification achieved, compared with 13 and 10 persons, respectively, in the methadone and propoxyphene napsylate groups ($p<.001$). Use of acupuncture and staplepuncture in outpatient clinics may be limited unless techniques can be found that will relieve withdrawal symptoms for a longer period than that observed in this study.

Observations by Wen and Cheung and others indicate that acupuncture and electrical stimulation will relieve opiate withdrawal symptoms for a few hours.[1-4] Sacks has attempted to develop a "built-in" acupuncturist by inserting a surgical staple into the concha, or inner wall of the ear, and by teaching heroin addicts to simply move the outer edge of the staple several times a day when heroin withdrawal symptoms become difficult to bear.[5] By use of this technique, called staplepuncture, an addict can remain ambulatory and carry on normal social functions. Reported here is a clinical trial of 18 heroin addicts who requested detoxification by acupuncture and staplepuncture as outpatients. Treatment results for this group are compared with results for two similar groups of 18 persons who received methadone or propoxyphene napsylate (Darvon-N®) for outpatient detoxification.

Methods

This study was conducted between February and April, 1975 at Community Health Projects,

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TABLE 1.—*Similarity of Acupuncture, Propoxyphene Napsylate and Methadone Groups*

	N=18		
	Acupuncture	*Propoxyphene Napsylate*	*Methadone*
Male	83.3%	77.7%	83.3%
Female	16.7%	22.3%	16.7%
Mean age, in years	29.7	28.5	27.1
Mean highest grade in school completed	9.9	11.3	11.6
Mean length of heroin use in years	8.6	9.1	7.8
Mean length of current daily heroin use in months	9.8	7.0	8.8

There was no statistically significant difference for any variable between the acupuncture, propoxyphene napsylate and methadone groups.

Inc., which is a health center located in West Covina, California. West Covina is a community in East Los Angeles County that is central to a heterogeneous population of low and middle income white and minority families. Community Health Projects, Inc. provides a program using several types of treatment for drug and alcohol abusers. Heroin addicts may select from a variety of outpatient treatment approaches, including the administration of methadone or propoxyphene napsylate.

To prepare for this study, Sacks, who developed the staplepuncture technique,[5] trained the research staff to carry out ear acupuncture, electrical stimulation and staplepuncture. An information notice was sent to referral sources in the clinic's catchment area and posted in the clinic to inform the addict population of the availability of acupuncture and staplepuncture treatment. Eighteen patients were admitted to the study who requested heroin detoxification by acupuncture and staplepuncture, and who met the following requirements: morphine sulfate in urine specimens; history of three months of daily heroin use; presence of fresh needle marks on the extremities; not pregnant, and no medical or psychiatric conditions requiring immediate treatment. Patients were informed that they could receive daily treatment with acupuncture, electrical stimulation and staplepuncture for a maximum of 21 days (Table 1). On the day the patient entered detoxification, a stainless steel surgical staple was inserted with a staplegun into the concha of each ear just posterior to the external auditory meatus. Patients were instructed, when away from the clinic, to move the staple up and down vigorously by hand when heroin withdrawal symptoms or heroin craving occurred. Each day when the patient attended the clinic, he was given a 15 to 20 minute treatment with electrical stimulation, which was applied to the staple by means of a constant-current stimulator that delivered byphasic square-wave pulses of 7 hertz and 0.2 milliampere. Additionally, acupuncture needles were inserted into the web between the thumb and second finger of both hands and into the occipital ridge behind both ears. Needles remained in place for the duration of electrical stimulation treatment.

Every day each patient filled out a questionnaire about the effectiveness of acupuncture and staplepuncture. A morphine withdrawal score similar to that of Himmelsbach was recorded each day just before and after acupuncture and electrical stimulation.[6] Withdrawal scores were determined by assessing the severity of the following signs and symptoms: gooseflesh, yawning, perspiration, lacrimation, rhinorrhea, myalgia or arthralgia, chills, nausea or vomiting, insomnia, anorexia, depression, diarrhea. The following system of scoring was used: 0 = absent; 1 + = mild; 2 + = moderate; 3 + = severe. A urine specimen was collected under observation when the patient began detoxification and four days later. Specimens were analyzed for morphine sulfate in order to determine if the patient had ceased heroin use and detoxification was successful.

Outcomes for these 18 patients were compared with those for 18 consecutive patients in whom detoxification had been accomplished in the same clinic by the same staff with methadone and with propoxyphene napsylate. The patients in the comparison groups had the same admission criteria as did those in the acupuncture and staplepuncture group (Table 1). Principal measurements evaluated in the acupuncture-staplepuncture and comparison groups were: daily withdrawal score; days retained in treatment, and number of patients in whom findings in tests on urine changed from morphine sulfate positive to morphine sulfate negative.

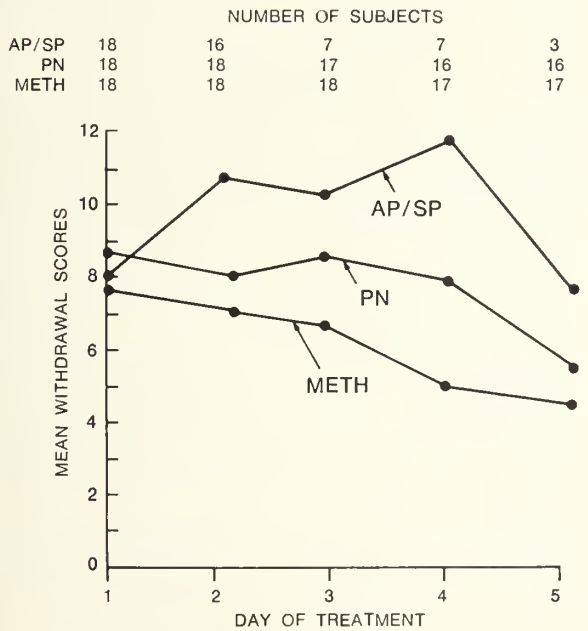
Results

Patients began to seek admission to the study within 10 days after availability notices were distributed. Four of 18 (22.2 percent) persons stated they sought acupuncture and staplepuncture treatment because they did not accept or would not enter a residential program or one in which methadone or propoxyphene napsylate was administered.

Retention of acupuncture patients was low. Only three (16.7 percent) patients remained in treatment on the fifth day compared with 17 of 18 (94.4 percent) methadone and 16 of 18 (88.9 percent) propoxyphene napsylate subjects ($P < .001$) (Figure 1). In one (5.5 percent) patient, tests of urine showed a conversion from morphine positive to morphine negative. This compares with 13 of 18 (72.2 percent) in the methadone group and 10 of 18 (55.5 percent) in the propoxyphene napsylate group ($P < .001$).

All 18 subjects felt that acupuncture and electrical stimulation provided at least partial relief of withdrawal symptoms temporarily. Patients reported that acupuncture and electrical stimulation relieved withdrawal symptoms from 30 minutes to 18 hours with a mean of 6.94 hours and a mode of 2.0 hours. Relief from withdrawal symptoms was substantiated by morphine withdrawal scores recorded before and after acupuncture and electrical stimulation (Figure 2). The overall mean, daily withdrawal score for the first five days, before acupuncture and electrical stimulation, was 9.5 compared with a score of 2.3 immediately after treatment ($P < .001$). Mean withdrawal scores each day were significantly reduced at the $P < .05$ level after treatment. The overall mean withdrawal score (9.5) before electrical stimulation, however, was significantly higher than the overall mean daily withdrawal score before daily medication administration in the propoxyphene napsylate (7.6) and methadone (6.6) groups ($P < .05$) (Figure 1). Since only one patient remained in acupuncture-staplepuncture treatment on the sixth day, no reliable statement regarding withdrawal scores can be made after the fifth day.

Sixteen of the 18 (88.9 percent) patients returned to the clinic at least one time to report on the effects of staplepuncture. Hand manipulation of the inserted staple while the patient was out of the clinic was reported to at least partially relieve withdrawal symptoms by 7 of 16 (43.8 percent). Twelve of 16 (75.0 percent) patients found the staple manipulations to be somewhat painful. No ear infections were observed. Interestingly, 6 of 13 (46.2 percent) patients who reported using heroin during staplepuncture felt that heroin euphoria was less than normal. Two subjects never returned to the clinic after day one and staples were therefore not removed by the clinic staff. Whether these subjects experienced any positive or negative effects is not known.



AP/SP = acupuncture/staplepuncture group
PN = propoxyphene napsylate group
METH = methadone group

Figure 1.—Mean opiate withdrawal scores for three treatment groups*

*Withdrawal scores are shown only for the first five days of a scheduled 21-day program since only one subject remained in AP/SP treatment on day 6. Mean withdrawal score for the AP/SP group was significantly higher at the $p < .05$ level on days 2-5.

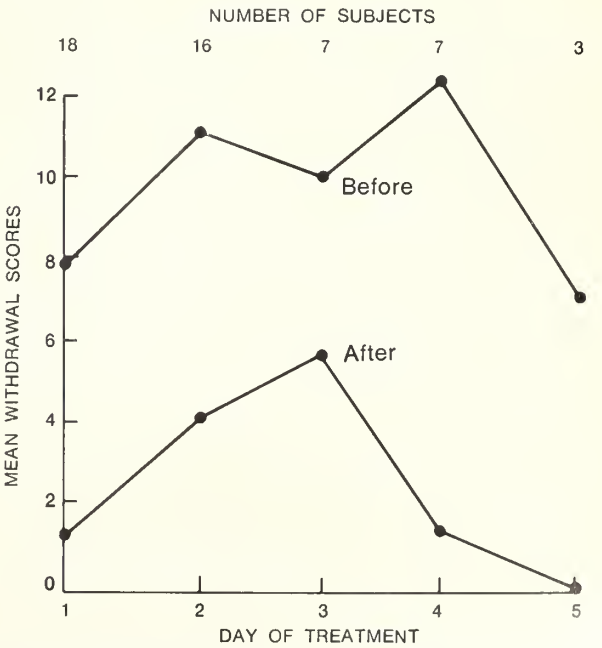


Figure 2.—Mean withdrawal scores before and after acupuncture treatment.*

*Withdrawal scores are shown for only the first five days of a scheduled 21-day program since only one subject remained in treatment on day six. Mean withdrawal scores for each day were significantly reduced at the $p < .05$ level after treatment.

Comment

Results of this study indicate that acupuncture and electrical stimulation will significantly relieve symptoms of heroin withdrawal for a temporary period. Some reports have previously reported this with human subjects, and Ng and co-workers have shown this in a controlled laboratory study with animals.[7] The physiological basis for these observations is entirely unknown. Staplepuncture may also have relieved heroin withdrawal since 7 of 16 (43 percent) patients reported at least some positive effects, although it is possible that similar results could have been accomplished with the use of a placebo. It recently has been shown that acupuncture probably acts as a placebo in treatment of chronic pain.[8] Placebo effect, however, may be a positive asset in patient care.[9] If our subjects had been inpatients and acupuncture and electrical stimulation had been administered more than once per day, detoxification would undoubtedly have been achieved in most of these patients since all reported at least temporary relief of withdrawal symptoms following acupuncture and electrical stimulation. In only one outpatient in this study, however, was detoxification accomplished as indicated by urine test findings changing from morphine sulfate positive to morphine sulfate negative. It is usually difficult for patients to attend an outpatient clinic more than once a day to receive treatment, and this appeared to account to a great extent for the poor patient retention in the program and the low detoxification rate observed. Unless an acupuncture-staplepuncture technique can be found to extend the time that withdrawal symptoms are relieved, it is unlikely that acupuncture-staplepuncture treatment will achieve widespread use in outpatient clinics. Acupuncture and electrical stimulation appear to have more potential for inpatient use since treatments can easily be given more than once a day.

It is not possible to conduct a double-blind study using acupuncture and staplepuncture on humans and therefore results for the patients in this study were compared with those for 18 patients in whom detoxifification was carried out using methadone and propoxyphene napsylate in the same clinic with the same staff. Nevertheless, all nonblind studies make it possible for staff bias to influence subjective observations and treatment outcome. Retention rates, morphine withdrawal scores and rates of conversions from morphine sulfate positive to morphine sulfate negative on tests of urine were superior in the methadone and propoxyphene napsylate groups. Four (22.2 percent) patients, however, sought acupuncture-staplepuncture treatment because they did not accept methadone or propoxyphene napsylate as treatment agents. For this reason, acupuncture and staplepuncture may be considered an outpatient alternative for addicts who do not accept available chemotherapeutic agents. Acupuncture, electrical stimulation and staplepuncture were administered to patients in this study by a physician and nurses who were briefly trained and not particularly expert in the techniques. It is possible that treatment outcomes for patients might have been improved if treatment had been given by clinicians who were more skilled in the art of acupuncture and staplepuncture. Furthermore, treatment outcomes may have been better if acupuncture and electrical stimulation had been administered for a longer period or given at more body sites.

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Medical PROGRESS

Detection and Management of Deep Vein Thrombosis

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The accuracy of diagnosis of deep venous thrombosis is significantly improved by combining clinical evaluation with other adjunctive methods, especially fibrinogen uptake tests, technetium scans, Doppler techniques and phlebography. Using these studies, early treatment with intravenous administration of heparin can be begun and in selected cases with long-term risks, warfarin is often useful. These same drugs, in different dosage schedules, may also be helpful as prophylaxis. With these methods of treatment, thrombectomy and caval interruption are required less often. If interruption of inferior vena cava flow becomes necessary, several new methods utilizing intracaval filters are proving to be very useful.

SEVITT AND GALLAGHER[1] examined an unselected group of fatally injured patients and found that in 60 percent deep vein thrombosis was present. They also noted deep venous thrombosis in more than 80 percent of elderly patients who died after having a fractured femur. Subsequently they showed that deep vein thrombosis occurred in 30 to 60 percent of patients after general surgical operations, and in up to 50 percent of patients in whom orthopedic operations on the lower extremities were being carried out. As has been emphasized by Skillman,[2] pulmonary embolism is a frequent occurrence after surgical operation, is one of the major causes of death after serious medical illnesses and is the greatest single cause of maternal deaths due to childbirth.

Pathophysiology

More than a hundred years ago Virchow[3] postulated that venous thrombosis occurred as a result of intimal damage, hypercoagulability and stasis of blood. Evarts[4,5] has recently suggested that two different types of thrombi occur: One is composed primarily of erythrocytes and fibrin, and characteristically is seen in areas of venous stasis. In the second type there is a white thrombus containing leukocytes, platelets and fibrin. The latter type of thrombus is found almost exclusively in association with rapid arterial flow, or in areas adjacent to injured vessel walls. Recent studies of venous thrombosis suggest that platelet activity may also trigger the formation of some venous thrombi, and that in some cases a small platelet nidus may precede activation of thrombosis.[5] Thrombus formation may therefore begin when platelets adhere to an altered intimal surface, or to exposed collagen in a damaged vessel wall. The subsequent activation of the intrinsic clotting mechanism produces the thrombus in a progressive reaction. There is persuasive evidence that this process may begin in valve cusps where there is stasis of blood, and therefore less effect of dilutional factors.[6] Changes in platelet adhesiveness occur during operation, after injury and in association with certain illnesses. In fact, results of

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studies of deep venous thrombosis have occasionally showed the presence of thrombi early during the surgical procedures.

Kakkar and his co-workers[7] have suggested that venous thrombosis usually starts in the tibial veins and the soleal sinuses, and then extends proximally into the popliteal, femoral and iliac veins. A dissenting view is taken by Mavor and his colleagues[8] who suggest that about two thirds of all pulmonary emboli arise from the ileo-femoral segment; they therefore consider these lesions to be primary. Kakkar and associates,[7] utilizing studies of deep venous thrombosis based on iodine-125 labeled fibrinogen scanning, showed that in approximately 35 percent of patients in whom localized increased radioactive counts persisted for more than 72 hours, there subsequently was extension of the clot into the popliteal and femoral veins. When this extension occurred in their study, the chance of a pulmonary embolus developing was approximately 40 percent. According to these workers, in those patients in whom clots were present only in the tibial or soleal veins, pulmonary embolism was very unlikely to occur. These data therefore strongly suggest that deep venous thrombosis may begin in the calf veins, but does not pose great danger to a patient until the clot extends into the femoral and iliac veins.

Diagnosis

The unreliability of clinical examination results in the detection of deep venous thrombosis is well known, but certain physical findings are helpful in establishing its presence. Edema of the ankle and leg, calf tenderness, tenderness in the popliteal and femoral areas, and a positive Homan's sign are considered characteristic of deep vein thrombosis. Findings on correlated studies suggest, however, that more than half of the patients with deep vein thrombosis diagnosed by other methods will be missed by clinical examination alone, and therefore adjunctive diagnostic techniques must be used.[2]

Ascending contrast phlebography is considered the most sensitive and complete of the tests and has been used to visualize the entire venous system of the lower extremity, iliac veins and vena cava. Other procedures used to diagnose venous thrombosis are compared with contrast phlebography as a standard, but because of the cost, risk and time, phlebography is not considered by most investigators to be a satisfactory screening technique. Many clinicians believe that phlebography should be reserved for patients in whom there are clinical signs and symptoms strongly suggestive of deep vein thrombosis, and in whom results of other less specific tests are equivocal. Phlebography is therefore particularly useful in specifically identifying deep vein thrombosis, excluding superficial phlebitis, cellulitis, hematomas and other conditions in which anticoagulation is not required.[9] It has been suggested that ascending phlebography also should be used before any operative procedure which incorporates interruption of the vena cava. In these cases contrast phlebography may establish the continued presence of potentially lethal venous thrombi, and may therefore offer compelling indications for operative intervention. Complications of ascending contrast phlebography are few, and are generally restricted to allergic reactions to the contrast media, localized phlebitis and hematoma at the site of injection, and, rarely, deep vein phlebitis. Pulmonary embolism occurring with ascending phlebography is extremely rare.

Numerous noninvasive techniques useful in the diagnosis of deep venous thrombosis have been proposed, including impedance plethysmography, phleborrheography, ultrasonic velocity flow detection, iodine-125 labeled fibrinogen scanning and radionuclide studies. Impedance plethysmography was described by Mullick and associates,[10] and is based on the principle that venous blood volume and the electrical impedance in the legs change with respiration if the venous system in the lower extremity is patent. When the test result is positive and compared with that from ascending contrast phlebography, the reliability appears to be approximately 90 percent, but when impedance plethysmography gives negative findings, the accuracy is reported to be only 50 percent. Recent modifications in carrying out the test have been advocated in which external compression of the leg is used instead of respiratory excursions, and this is reported to have increased the sensitivity and accuracy.

Cranley and his associates[11] developed a plethysmographic technique for the examination of thigh and calf volume changes in response to compression of the calf or foot. They have named this technique phleborrheography, and in their initial reports of 304 limbs there were only three false negatives. In addition, of 227 limbs for which findings were normal on phlebograms, only four false positives were discovered. These initial re-

ports strongly suggest that this innovative technique will be of great value in the detection of deep vein thrombosis.

The Doppler ultrasonic velocity flow detector has been useful in the detection of deep vein thrombosis. Strandness and Sumner[12] reported that this technique accurately predicted deep vein thrombosis in more than 93 percent of 53 patients in whom either venographic studies or operations subsequently were carried out in order to confirm the diagnosis. Sigel and his co-workers,[13] however, report on 8,500 examinations done in more than 5,000 patients. In results of 248 examinations with concurrent phlebography the Doppler survey agreed in approximately 75 percent of the patients with limbs containing venous thrombosis. With this extensive experience these authors concluded that the method was valuable, but could not detect mural clots, nor expose clots when only tributory veins were involved, and patent collateral veins were present. They also emphasized that error may arise because of improper positioning of the probe, emptying the veins by gravity or compression bandages. They concluded that the Doppler velocity flow meter was particularly useful in detecting complete thrombosis involving the femoral and the iliac veins, especially when recent. This technique therefore has certain limitations and can not be reliably employed as a solitary method of examination.

Flanc, Kakkar and their associates[14] pioneered in the technique of utilizing fibrinogen tagged with iodine-125 in the diagnosis of deep vein thrombosis. The test requires that the radioactive fibrinogen be incorporated into newly forming thrombi; then the activity is detected by scanning the leg and thigh with a portable scintillation counter. This has proven to be an extremely useful and valuable test in the detection of deep vein thrombosis, but is not completely reliable in patients with established clots because it depends on incorporation of the labeled fibrinogen into the thrombus. It may be useful for the detection of iliac and pelvic vein thrombosis, but cannot be used immediately adjacent to areas of recent surgical wounds about the hip because of pooling and hematomas near the operative incision. It is the single most sensitive and useful noninvasive test in the diagnosis of deep venous thrombosis. It has been widely used in Europe but because of limited access to hepatitis-free fibrinogen it has not been used as frequently in the United States.

Pollak and his associates[15] studied deep vein thrombosis in a group of patients utilizing labeled fibrinogen, and venous imaging with technetium-99m (^{99m}Tc). Microaggregates of albumin incorporating technetium-99 are prepared to form particles 10 to 50 microns in size, and the solution subsequently injected into dorsal veins of the foot. Isotope distribution in the legs and pelvis is then detected by scintillation counters and photographed. In these same patients autologous fibrinogen is secured, and labeled with iodine-125, and injected into an antebrachial vein. Isotope localization is then detected with scintillation counters. These investigators utilized both of these tests in a series of 89 patients and concluded that an abnormal finding on technetium scan is accurate in more than 90 percent of cases, and 80 percent reliable in separating patients with venous disease from those who do not have deep vein thrombosis. They emphasized that false positives occur because any area of endothelial damage may trap aggregates, and thereby localize the isotope. They stated that the fibrinogen uptake test is considered to be 100 percent sensitive in differentiating active recent thrombosis from long-standing venous obstruction. They therefore concluded that use of a combination of these two tests offers reliable evidence as to the presence of deep vein thrombosis, and may obviate the necessity of carrying out contrast phlebography.

The proliferation of various tests proposed to assist in the diagnosis of deep vein thrombosis underscores the difficulty of accurate identification of patients with this disease. Fibrinogen uptake tests appear to be the most sensitive, and are considered by many workers to be extremely reliable in the detection even of small vein thrombosis. Plethysmographic techniques developed by Cranley and his associates[11] promise to be of great value, and perhaps will be more useful than impedance plethysmography. It is clear that the clinical evaluation is materially improved when combined with radionuclide studies, Doppler ultrasonic examinations, and especially if fibrinogen uptake tests are also used. All of these tests are compared with ascending contrast phlebography, and it is apparent that despite its invasive nature, use of phlebography may be required to resolve differences in interpretation of the various other tests.

Prevention of Deep Vein Thrombosis

Linton, Ochsner and others[9] for a number of years have stressed the function of the "peripheral

heart" in maintaining normal venous return and avoiding stasis. They have emphasized the importance of the soleal pump, elevation of the lower extremities, the maintenance of normal blood volume and plasma composition in reducing the incidence of stasis and venous thrombosis. Flanc and his co-workers[14] reported the results of an intensive program of prophylactic physical measures instituted in a group of 67 patients who were preoperatively instructed in active leg exercises. The subsequent diagnosis of deep vein thrombosis was based on a positive labeled fibrinogen uptake test. Of those elderly patients in whom major operations were carried out the incidence of deep vein thrombosis was 61 percent in the control group, but only 24 percent in the test group—a significant difference.

Tsapogas and his associates,[16] utilizing labeled fibrinogen scans, have reported a reduction in deep venous thrombosis by active exercises. In contrast, in a randomized study reported by Rosengarten and co-workers,[17] compression stockings in a group of 50 patients in whom elective general surgical procedures were being done could not be shown to be beneficial in preventing deep vein thrombosis.

Intermittent rhythmic compression of the legs produced by external pneumatic devices has been suggested as a useful substitute for the "soleal pump."[4] Although several early reports from these studies suggest that such procedures may be useful in preventing stasis, and perhaps deep venous thrombosis, there has not been sufficient experience to determine the true effects of the technique. These studies have generally been related to personal experience and do not reflect controlled scientific data, but it is reasonable to assume from the frequency of these reports and from the experience of many investigators that prevention of venous stasis is an important concept of prophylaxis against deep venous thrombosis.

Prophylactic Drug Therapy

Several drugs are known to prevent thromboembolism in high risk patients, and as Salzman[9] has emphasized, the evidence is most convincing for the case of warfarin and other oral anticoagulants. He and his associates reported that clinically detectable thromboembolic complications can be significantly reduced in patients with fracture of the hip if prophylactic warfarin is administered. In a prospective randomized study of thromboembolic disease following total hip replacement in 237 patients, Harris[18] reported that warfarin sodium and dextran 40 were equally effective in preventing fatal emboli. There were no statistically significant differences between the two agents. In this high-risk group of patients, clinically detectable thromboembolic disease occurred in 10 percent.

In contrast, Ritter and Hamilton[19] examined the effectiveness of warfarin and low dose heparin as thromboembolism prophylaxis in patients undergoing total hip replacement. In all, 380 consecutive cases of total hip replacement orthoplasties were divided into four groups for purposes of treatment and analysis. All patients were treated with mild elevation of the legs and elastic stockings, and they were encouraged to use their calf and thigh muscles. The diagnosis of venous thrombosis was made by clinical criteria, using the classic signs of calf tenderness, warmth, edema, Homan's sign and fever. One group of patients received sodium warfarin on the night of surgical operation, and beginning on the second day doses were given each day in an effort to maintain the prothrombin time at twice the control value. Group two received low-dose heparin as recommended by Kakkar and his colleagues, 5,000 units 2 hours before operation and every 12 hours postoperatively. Group three received low-dose heparin administered eight hours preoperatively, and group four had, in addition to the low-dose heparin, hydrocortisone given three times per day. The lowest incidence of thromboembolic phenomena occurred in patients receiving warfarin. The average blood replacement was highest in those patients given heparin two hours before operation. The study therefore suggests that oral administration of anticoagulants may be more effective in the prevention of thromboembolism in high-risk patients.

In a study of 514 patients receiving low molecular weight dextran, Evarts[4] stated that the expected incidence of deep venous thrombosis was reduced to 4.3 percent. In only five of the 514 patients did nonfatal pulmonary emboli develop, an incidence of 1 percent. Evarts therefore suggested that dextran 40 is the agent of choice in these patients, but other investigators take a dissenting view. Skillman and Salzman have emphasized that the complications and expense associated with use of dextran may detract somewhat from its usefulness. Salzman further stated that "dextran produces allergic reactions frequently, anaphylactic reactions occasionally, and renal

failure rarely." From these data, however, it is apparent that the prophylactic administration of warfarin sodium or dextran, or both, may be useful in the prevention of deep venous thrombosis in high-risk patients, although certain undesirable side effects may be encountered.

Kakkar, in an initial report concerning more than 4,000 patients admitted to a prospective control study, suggested that low-dose heparin is the most effective prophylactic agent.[2] In these patients, 5,000 units of aqueous heparin was administered subcutaneously two hours before and immediately after operation, and at eight hour intervals thereafter. The beneficial effects seem to be the result of the potentiation of factor Xa inhibitor, a naturally occurring anticlotting factor. According to these workers the regimen is useful in patients in whom general surgical operations are being carried out, but is not as effective in high-risk patients in whom orthopedic procedures have been done. The results reported in approximately 4,000 of the 20,000 patients in this prospective study are encouraging: only one case of pulmonary embolism in the heparin-treated group has been reported as compared with 12 in the control group.

In a coded, prospective study by Covey, Sherman and Baue,[20] low-dose heparin was found not to be as effective as other means in preventing thromboembolic phenomena. These workers studied the cases of 105 patients randomly divided into control and treated groups, utilizing low-dose heparin as described by Kakkar. Deep venous thrombosis was detected by daily fibrinogen scanning, and then confirmed by ascending contrast phlebography. Both groups were comparable by age, sex, type of operation and incidence of previous thromboembolism, and also by presence of myocardial or cerebral vascular disease, or both. In this study blood loss was not increased in the treated group. The incidence of deep venous thrombosis was 8.6 percent for the total group, 7.5 percent in the heparin-treated group and 9.6 percent in the control group. There was one pulmonary embolus seen on scan in one of the patients in the control group. The authors concluded that this study showed no increased hemorrhage in heparin-treated patients, but neither did it show a beneficial effect of heparin administration in preventing deep vein thrombosis.

Salzman and his associates[18] reported on the prophylactic effect of dipyridamole, aspirin and dextran in patients in whom hip orthoplasty was done. Dipyridamole was eliminated from the study early because of the 34 patients being treated with this drug, thromboembolic complications developed in 26. The incidence of thromboembolism in the group treated with aspirin and dextran was approximately the same as in those patients treated with warfarin, and the authors concluded that in all the patients significant protection was conferred by administration of these drugs. The report by the National Research Council in Britain, covering 303 patients in whom elective operations were done, gives findings at variance with these data in that no protective effect of aspirin administration could be shown, utilizing labeled fibrinogen scans to detect deep venous thrombosis.[2] Because of such discrepancies, use of primdopyrimidine compounds and administration of the nonsteroidal antiinflammatory agents such as aspirin cannot at present be recommended as effective prophylactic antithrombotic measures under currently employed protocols.

These conflicting reports as to the effectiveness of the prophylactic measures are difficult to reconcile, but appear to be the result of varying methods of study, different dosage schedules, variations in types of drugs used, nonstandardized methods of detecting deep vein thrombosis and inadequately controlled data. From these studies, however, certain conclusions seem warranted. It appears that in older patients, in patients with a history of deep venous thrombosis or pulmonary embolism, or in patients in whom the presence of varicose veins, obesity or malignancy is found deep venous thrombosis is likely to develop. In these high-risk patients prophylactic low-dose subcutaneous heparin, or warfarin sodium may be useful. When contraindications to prophylactic anticoagulation are present, the fibrinogen scanning technique is useful in the early detection and treatment of deep venous thrombosis.

Superficial Phlebitis

In patients with phlebitis confined to the superficial venous system, anticoagulant therapy rarely will be required. Elevation, rest and elastic compression will usually be successful in the management of these problems. In some patients superficial phlebitis extends above the knee, and it has been suggested by Cranley and others[11] that ligation of the saphenous vein at its entrance into the common femoral vein is effective in treating these patients. This procedure often produces

early resolution of the processes, and may prevent thrombotic extension of the deep venous system. It is carried out under local anesthesia and usually reduces pain and morbidity within the first 48 hours after operation, and allows an early discharge from hospital.

Deep Vein Thrombosis

Deep vein thrombosis is best treated by venous infusion of heparin. In the regimen described by Dale,[9] aqueous heparin—5,000 international units—initially is administered by intravenous push. If a continuous intravenous infusion of heparin solution is then administered, a patient of average weight would receive approximately 12,500 units of heparin in 500 ml of 5 percent dextrose solution every eight hours. A continuous infusion pump is desirable, and levels of heparin activity are usually monitored by measuring activated whole blood partial thromboplastin time at least once a day during therapy. Heparin sensitivity increases as administration of the drug is continued and the thrombotic process resolves, and it is often necessary to subsequently readjust the dose to lower levels. Most clinicians maintain an activated whole blood partial thromboplastin time of approximately twice the control level.

Salzman and Hume and others[9] propose that in a patient with deep venous thrombosis, warfarin sodium be given concomitantly with heparin administration, and that the disorder slowly be brought under control with the use of the orally given anticoagulant. The usual practice is to give both agents for ten days, and then subsequently the orally administered medication is continued for several months if predisposing conditions leading to the deep venous thrombosis cannot be eliminated. Initially the prothrombin time is checked every day during the first week, and subsequently two or three times a week. A dissenting view is taken by Dale,[9] however, who does not use orally given anticoagulants concomitantly with the heparin infusion, nor does he use warfarin in patients who cannot be followed very closely because of the risk of dangerous bleeding. He also describes seeing acute exacerbations of venous thrombosis, and even fresh clots in patients in whom adequate anticoagulation is achieved using warfarin.

Following a major surgical procedure, anticoagulants must be given judiciously, and most workers suggest that they can safely be started within 6 to 12 hours after the operation is concluded. This may not be true in patients in whom orthopedic procedures or radical prostatectomies have been done, or in patients in whom there is danger of retinal or intracranial hemorrhage. Most clinicians combine anticoagulant therapy with elevation, and in some instances elastic stockings when venous abnormalities are present. Ambulation is usually begun as soon as symptoms permit because it is desirable to return the venous circulation to normal as soon as possible, while the patient is under the protection of intravenously given heparin. Once the swelling is resolved and the pain permits, full ambulation is therefore begun and when leg swelling has decreased sufficiently, measurements for a custom-fitted elastic stocking are taken.

Thrombolytic Agents

Streptokinase and urokinase were utilized in a cooperative study in the evaluation and treatment of pulmonary embolism, and have been shown to hasten the lysis of clots in patients with established pulmonary emboli.[2] Although the morbidity and mortality in this group of patients were not significantly changed, use of these thrombolytic agents may shorten the course of venous occlusion, and perhaps reduce postphlebitic phenomena. Silver[21] has shown that if heparin is given in sufficiently large amounts clotting is inhibited and thrombolysis is augmented. Accelerated lysis induced by these agents may therefore be important adjuncts in managing patients with deep venous thrombosis and massive pulmonary embolism, but they cannot be administered in the immediate postoperative period to patients after serious trauma has occurred, or after extensive surgical procedures. These agents may be useful in certain cases in which massive thrombosis is present if the risks are not extended by a recent surgical procedure.

Operative Procedures

Iliofemoral venous thrombectomy as originally described by Mahorner, Haller and others is useful in the treatment of patients with phlegmasia serulea dolens.[22] Of patients in whom massive iliofemoral venous outflow block has occurred, amputation is required in almost a third, and without treatment approximately one in four will die. It has been shown in other patients with less serious iliofemoral venous thrombosis that elevation, rest and intravenous heparin administration are quite effective, and surgical operation is

often not required. When there are contraindications to the administration of anticoagulants or there is threatened tissue loss, venous thrombectomy may be very useful—and often produces a dramatic response. Some surgeons suggest that vena cava interruption should accompany this operation, but others believe that if complete thrombectomy is done early in the disease, thromboembolic phenomena are very uncommon.

Contrast phlebograms, made at varying intervals after iliofemoral venous thrombectomy, have shown that in many people the operation has failed and the segment of vein operated upon has reclotted.[23] Additionally, the proposed aim of preserving valvular function by early operation has not been consistently accomplished. In fact, late phlebographic studies show that the incidence of postphlebitic problems is quite similar in patients treated with heparin and in those treated with operation. For these reasons most surgeons limit iliofemoral venous thrombectomy to patients who are threatened with loss of life or limb.

Interruption of Inferior Vena Cava

Silver[21] reports a 3 percent incidence of recurrence of pulmonary emboli in patients treated with a continuous infusion of intravenous heparin, a recurrence rate comparing favorably with those results obtained with caval interruption. Most clinicians now believe that caval interruption should be undertaken only in those patients in whom heparin therapy has failed, those in whom anticoagulation cannot be done because of concomitant illnesses such as bleeding ulcers, patients in whom there have been recent operations upon the brain or retina or people in whom orthopedic operations have been carried out recently. A documented recurrence of pulmonary embolization in patients adequately treated with intravenous heparin is generally considered by most clinicians to be an indication for caval interruption. The recurrence of small emboli under adequate therapy is also considered an indication for caval ligation. Septic emboli are now usually treated by a combination of heparin and appropriate antibiotics, because ligation procedures have failed to completely trap these very small emboli which are able to traverse collaterals and eventually reach the pulmonary circulation.

Inferior vena caval ligation has been the most commonly employed method of caval interruption, but numerous methods of partial interruption have been advocated as being effective, and are said to be accompanied by a lower incidence of venous thrombosis. These methods of partial interruption include narrowing the cava with Teflon® clips, compartmentalization or plication with sutures, or construction of a filtering grid across the lumen of the cava. Recently innovative intracaval techniques have been introduced in the form of fenestrated catheters, balloon catheters, metal cones and an umbrella that has been extensively employed over the past few years.[2,22] The Mobin-Uddin[24] umbrella is a fenestrated or solid Silastic umbrella which under local anesthesia may be inserted into the infrarenal cava through the ipsilateral internal jugular vein. With phlebographic and fluoroscopic control it can be accurately positioned below the renal veins. The procedure is less difficult than some other methods, and does not require major surgical operation. Slow progressive occlusion of the vena cava is supposed to ensue following insertion of the umbrella, but on occasion abrupt occlusion occurs and in some instances clots have been shown to be present on the cardiac side of the umbrella. Erosion out of the vena cava into the ureter or other viscera, or into other vessels has occurred on rare occasions. In most hospitals when the indications for caval interruption arise insertion of the Mobin-Uddin umbrella is considered an extremely useful method, carrying a low morbidity and mortality. Mobin-Uddin has suggested that before the umbrella is placed, ascending contrast phlebography should be done to be certain that the continuing risk of pulmonary emboli is present, because although the procedure is less risky than other major operations, it is attended by a significant number of complications.

Simon, Salzman and Freiman[25] recently reported the development of an innovative technique of inferior vena cava interruption which employs a metal wire that changes shape depending on the temperature to which it is subjected. This experimental filter is made of a nickel-titanium alloy called Nitinol, and exposure to a warm temperature above 32°C causes it to return to a shape previously imprinted. The filter can therefore be introduced into the vena cava via a standard angiographic catheter in the form of a straight wire bathed in a cooling solution. Upon reaching the vena cava the cooling solution is stopped and the wire encounters blood at body temperature, and immediately assumes the shape imprinted at the cool temperature. It then locks itself into position at the desired level of the vena

cava. This filter may prove to be safer than others currently used. It requires less of a surgical procedure than that necessary for the introduction of a Mobin-Uddin umbrella. The preliminary data in the experimental laboratories are extremely encouraging and further testing is in progress.

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Treatment of the Grossly Contaminated Surgical Wound

DR. POLK: If there is any doubt whatsoever, the method of treatment of a wound is by delayed primary closure. I don't think it has ever been improved on as a method for dealing with likely infection. You might use antibiotics in addition, but I think it (primary closure) really is the fail-safe mechanism.

DR. DUNPHY: I think the other message is that if the wound is heavily contaminated, just leave it open. There is an infection rate to the delayed closure . . . The most important thing is not to put a suture through it with the idea that you're going to close the stitch at that time, because that one suture is a potent source of infection introduced at the time of operation. The incidence of infection, when you tighten that, is bound to be high. And I think the same goes for using little wicks. You put a little wick in a wound, or you can put a drain in a wound because you're worried about bleeding, about leak . . . But if you really feel you have a contaminated wound and you put a wick in, . . . it's the surest way to encourage sepsis around it.

—HIRAM C. POLK, JR., MD, *Louisville*
J. ENGLEBERT DUNPHY, MD, *San Francisco*
Extracted from *Audio-Digest Surgery,* Vol. 22, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Specialty Conference

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From the Departments of Pediatrics and Radiology, University of California, San Diego, School of Medicine, and University Hospital, San Diego.

Refer to: Schneider JA, Weller M, Gersh ES, et al: Rickets—University of California, San Diego, and University Hospital, San Diego (Specialty Conference). West J Med 125: 203-211, Sep 1976

Rickets

WILLIAM L. NYHAN, MD, PH D:* Rickets is one of the classic problems in pediatrics. It illustrates very clearly the close interaction between the processes of growth and development and disordered physiology that make disease special in the pediatric age group. The discovery of vitamin D and its widespread application throughout the world was a major advance in public health which converted a very common disorder into a rarity. Nevertheless, it is not true that we see more patients with vitamin D-resistant rickets than with vitamin D-deficiency rickets. The classic disorder is still with us. In this conference we shall review some of the classic findings and some of the new information in this area. The first patient will be presented by Mr. Gersh.

ELLIOTT S. GERSH:† Case 1. A 2-year-old black boy was referred for evaluation of bilateral bowed legs. When the patient was an infant he had been noted to be bowlegged. However, several other members of the family were mildly bowlegged and this was not thought to be significant. The bowing became more pronounced when the patient began to walk at 13 months of age. He was seen at the age of 19 months at Children's Orthopedic Hospital in Seattle where findings on x-ray studies were suggestive of rickets.

The patient was the product of a normal pregnancy and delivery. The birth weight was 2,667 grams (5 lb 14 oz). There were no significant problems or illnesses. The infant was breast fed until he was 17 months old, but he also ate solid foods and had a good appetite. The history was that he was given vitamins A, D and C in the form of Tri-Vi-Sol® from 6 to 12 months of age.

The patient's father, three paternal uncles and a 5-year-old brother had mildly bowed legs. The father was examined and the findings were minimal.

On physical examination the patient was found to be healthy and active. The only abnormal findings were the bilateral tibial bowing and a height of 81.3 cm (32 in). This was a height age of 18 months at a chronological age of 27 months. Laboratory studies in Seattle had shown the concentrations of calcium, phosphate, electrolytes and blood urea nitrogen (BUN) as well as an amino acid screen of the urine to be normal. The alkaline phosphatase was slightly elevated. On x-ray films, signs of active rickets as well as the old deformities were seen (Figure 1). The patient was felt to have vitamin D deficiency. He was treated with 10,000 units of vitamin D daily. On repeat x-ray studies made during a six month period, progressive healing was noted.

DORIS TRAUNER, MD:‡ Case 2. A 2-month-old black boy was admitted because of jitteriness and left-sided jerking. The patient was well until the day of admission when three brief episodes of

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Figure 1.—(Case 1) Rickets already healing at the time of the first radiograph continued to heal progressively over a period of six months. There are fractures of the distal tibias. Bowing deformity of tibias is prominent but the fibulas and femurs are also bowed. This bowing was still present after six months.

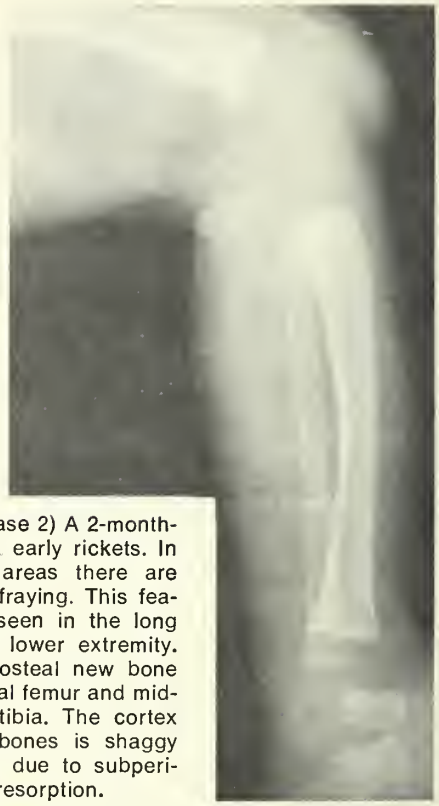

Figure 2.—(Case 2) A 2-month-old child with early rickets. In metaphyseal areas there are cupping and fraying. This feature is best seen in the long bones in the lower extremity. There is periosteal new bone along the distal femur and midshaft of the tibia. The cortex of the long bones is shaggy and irregular, due to subperiosteal bone resorption.

clonic movements of the left arm and leg occurred which lasted approximately 3 to 4 seconds. The child was brought to another hospital where on lumbar puncture cerebrospinal fluid was found to be normal. Phenobarbital (Nembutal®) was given and the patient was transferred to University Hospital.

The patient was born at 36 weeks gestation by cesarean section because of cephalopelvic disproportion and two previous sections. Birth weight was 2,213 grams (4 lb 14 oz). The baby was in hospital for seven days for temperature instability and inability to gain weight. The baby was fed Enfamil® plus iron approximately 20 to 30 oz per day. Baby cereal was started at 2 weeks of age, and vitamins A, D, C and fluoride (Tri-Vi-Flor®) were started at 6 weeks.

Family history and review of systems were noncontributory.

On physical examination, the infant was found to be well-developed but lethargic. Body weight was 3,376 grams (7 lb 7 oz). The fontanelle was not tense. The pupils were equal and reactive to light, and the fundi were benign. A grade III/VI holosystolic murmur heard at the left sternal border radiated to the axilla and pulmonic area. The baby had a poor suck and Moro reflex. The deep tendon reflexes were 2+ and equal bilaterally. There was a pronounced and sustained clonus. Chvostek and Trousseau signs were positive.

Initial laboratory studies gave the following values: hemoglobin, 9.8 grams per 100 ml; hematocrit reading, 28 percent; leukocyte count, 10,400 per cu mm with 35 segmental polymorphonuclear cells, 4 band forms, 56 lymphocytes and 5 monocytes. The serum concentration of calcium was 5.4, magnesium 1.9 and phosphate 4.8 mg per 100 ml. The alkaline phosphatase value was 16 units (normal adult value 2 to 5 units). Electrolytes were normal, as were the total protein, glucose and BUN levels. The urinary calcium level was 2.7 mg per 100 ml. X-ray studies showed early rickets to be present (Figure 2).

The patient was immediately treated with 400 mg of calcium gluconate given intravenously. For approximately one week the infusion was continued and the dose was increased to 1,500 mg of elemental calcium per day in order to maintain normocalcemia. Gradually he could be weaned to a regimen of 600 mg of calcium and 1,000 units of vitamin D given orally. Two months later, the serum calcium level was 9.7 and the phosphorus level was 6.1 mg per 100 ml. The

patient was receiving 2 tsp three times a day of glubionate calcium (Neocalglucon®) and 1,000 units of vitamin D per day. Findings on x-ray studies of the wrists showed healing of the rickets.

Case 3. A 4-month-old white boy was referred to University Hospital because of left-sided seizures which had begun at three o'clock that morning.

The patient was born after approximately 28 weeks of gestation to a gravida 2, para 2, 40-year-old woman who had had two episodes of vaginal bleeding before the delivery. The birth weight was 1,007 grams (2 lbs 12 oz) and the infant was kept in a nursery for approximately three months. During that time his problems were hyperbilirubinemia with values up to 15 mg per 100 ml, which was considered to constitute physiological jaundice, and intermittent apnea responsive to stimulation which lasted into the fourth week. He was discharged one month before this admission weighing 2,156 grams (4 lbs 12 oz). He did well until the morning of admission when a left-sided focal seizure occurred which lasted approximately half an hour. A lumbar puncture carried out in a physician's office showed 6 mononuclear cells. Several left-sided seizures occurred in the office, each lasting one to two minutes. Treatment was carried out with paraldehyde, three times, and with phenobarbital. The infant was then transferred to University Hospital.

Figure 3.—(Case 3) A lateral radiograph of the chest showed accumulations of poorly-mineralized osteoid at the costochondral junctions, producing the classic "rachitic rosary" which was readily apparent on physical examination.

On arrival he was awake, but lethargic. He held his head in a slightly opisthotnoic position. He had infrequent, brief left focal seizures involving the left arm and the mouth.

The feeding history was pertinent in that he had been receiving breast milk and bananas. In the nursery he had been fed Enfamil for one month, and he was breast fed after that. He had received no vitamin supplements. He had had bilateral inguinal hernias and an umbilical hernia. His past history was otherwise noncontributory, as was the family history.

On physical examination, head circumference was found to be 39 cm, which was less than the third percentile for 4 months of age, but at the 90th percentile for 1 month of age, which was his age from the end of a normal gestation. The anterior fontanelle was large and full, and a widely spread metopic suture came down to his nose. There were a 1.5 cm umbilical hernia, and bilateral inguinal hernias. Head control was poor but he had a good suck, a full Moro reflex, good grasp and a positive stepping response.

Results of laboratory studies showed the presence of anemia with a hemoglobin value of 8.1 grams per 100 ml, a hematocrit reading of 24 percent and a reticulocyte count of 2 percent. Serum levels of electrolytes, glucose, BUN and creatinine were normal. The alkaline phosphatase value was 44 units (normal adult value 2 to 5 units). The serum concentration of calcium was 6.1, magnesium 2.0 and phosphate 5.2 mg per 100 ml. On an electrocardiogram, a prolonged QT interval was noted which was compatible with hypocalcemia. Electroencephalographic findings showed dysrhythmia grade III with minimal generalized slowing and generalized spiking in the right temporal region. Right upper lobe and right middle lobe infiltrates were seen on an x-ray film of the chest. At the costochondral junction, florid rickets was noted (Figure 3). On x-ray films of the skull, a profound lack of ossification in the calvarium was noted. Diploic sinuses were defin-

able only in the fontanelle and occipital regions. The entire base of the skull was poorly ossified.

The infant was treated with parenterally given antibiotics for the pneumonia and parenterally and orally administered calcium to stop the seizures and to correct the hypocalcemia. There was no recurrence of seizures. On supplementation with 400 units of orally given vitamin D per day, the serum concentration of calcium returned to normal levels. Two weeks after vitamin D therapy was started, the serum level of calcium was 9.4 mg per 100 ml. Two months later the value was 10.6 mg per 100 ml and the phosphate was 7.5 mg per 100 ml. On supplementation with iron, given orally, the reticulocyte count rose and the hematocrit reading returned toward normal levels.

MICHAEL WELLER, MD:* Using the three cases presented and some others, the radiologic findings in rickets will be reviewed, as well as the physiology responsible for producing the classical radiologic pattern.

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Figures 4 and 5 provide an example in which the rickets was considerably more florid than in the cases presented. It serves as a classical model. There is pronounced deossification of all the long bones. In addition, in the metaphyseal regions of the long bones cupping and fraying are seen to be present (Figure 4). The growth plates were considerably widened. In the metaphyses, normally the area of greatest density—the zone of provisional calcification—is replaced by a zone of lucency due to the absence of fully mineralized cartilage and bone.

In the first few weeks of the rachitic process, all that one may see radiologically is generalized rarefaction of bone. Soon, the normal progression of endochondral ossification slows and, as cartilage cells in the growth plate mature and begin degenerating, calcium is no longer available for deposition in the zone of provisional calcification. Large amounts of degenerating cartilage and immature, unossified osteoid accumulate, resulting in widening of the normally radiolucent growth plate. Because the process is not uniform, a

Figure 4.—Dietary rickets. In the metaphyseal areas at the wrist and knee there is widening of the growth plates with loss of normal density in the zone of provisional calcification. The process is irregular, leading to a frayed appearance. Cupping is present uniformly, but most pronounced in the distal ulna and proximal fibula.

"frayed" appearance of the metaphysis results. "Cupping" is due to continuing *periosteal* new bone formation at the periphery of the metaphysis just below the growth plate, which begins to surround the bulky osteoid accumulating in this area.

Cupping is seen best in the distal ulna, tibia and fibula, and at the distal radius only quite late in the disease. At times, the bulky knobs of poorly mineralized osteoid in the metaphyses cast soft tissue density on the radiograph. These collections are responsible for the palpable swollen joints and costochondral junctions (the "rachitic rosary").

Longitudinal growth of bone is accomplished by the process of endochondral bone formation. The periosteum is also capable of bone production. This latter process usually continues even after endochondral bone formation ceases, at least for a while. This may be manifest as lamina of periosteal new bone. Finally, periosteal new bone formation ceases also, and subperiosteal bone *resorption* begins, giving the entire bony diaphysis a finely irregular, or shaggy, appearance.

With therapy, through the direct action of vitamin D, circulating calcium and phosphorus are incorporated into the accumulating immature osteoid, and mature bone is formed. Radiologically, this results in the reestablishment of a new dense zone of provisional calcification, in a location where it would have been, had rickets not supervened (Figure 5). The lucency of the radiologically widened growth plate then begins to fill in gradually, the fraying and cupping are gradually remodeled, and the normal smooth tapered contours restored. The zone of lucency immediately shaftward from the *new* dense zone of provisional calcification may be reminiscent of leukemia, unless one notices the residual cupping and fraying, and is aware of the clinical history.

Bowing of the lower extremities may occur because of loss of the structural integrity of bone (Figure 1). This usually resolves in time with treatment in dietary rickets. Residual bowing is common in renal rickets. In the first patient, the 2-year-old child described this morning, radiographs showed progressive healing of the rickets over several months after the initiation of vitamin D therapy (Figure 1). The bowing was still prominent after six months.

The second patient described this morning was a 2-month-old child who presented with seizures. Radiographs of the skull provide the first evidence of profound deossification. Examination of the long bones confirms this and shows the characteristic cupping and fraying in the metaphyseal areas. This is most pronounced in the upper extremities

Figure 5.—Sequential healing of rickets following treatment with Vitamin D. (Same patient as in Figure 4.) These changes occurred over a period of four months. There is progressive restitution of the metaphysis with initial deposition of mineral closest to the epiphysis. The lucent zone in the metaphysis gradually fills in and disappears with continued healing.

in the distal ulnas. In the lower extremity it is prominent in the tibias, and fibulas (Figure 2). With therapy, the zone of provisional calcification begins to regain its original density and periosteal new bone formation blends with the cortex of the diaphysis.

The third patient, a 4-month-old infant, also presented with seizures, and radiographs show profound lack of bone in the calvarium, even in the petrous portions of the temporal bones, normally the most dense area in the skull of the infant. A large amount of unmineralized immature osteoid is present at the costochondral junctions, producing a rachitic rosary (Figure 3). The long bones show cortical thinning and irregularity, in addition to rachitic metaphyseal changes. There is irregularity in the metaphyses, well shown in the distal femur, proximal and distal tibia, and fibula. Cupping and fraying are most obvious in the distal tibia and fibula.

A final example of severe rickets is noted in twin chimpanzees from the San Diego Zoo (Figure 6). Changes are present that are identical to those described in the children presented this morning.

Vitamin deficiencies are rare today. Many food products contain vitamin supplements. The severe changes of rickets are seldom seen, and often the initial radiographs of a patient show evidence of partial, although insufficient bony response to treatment.

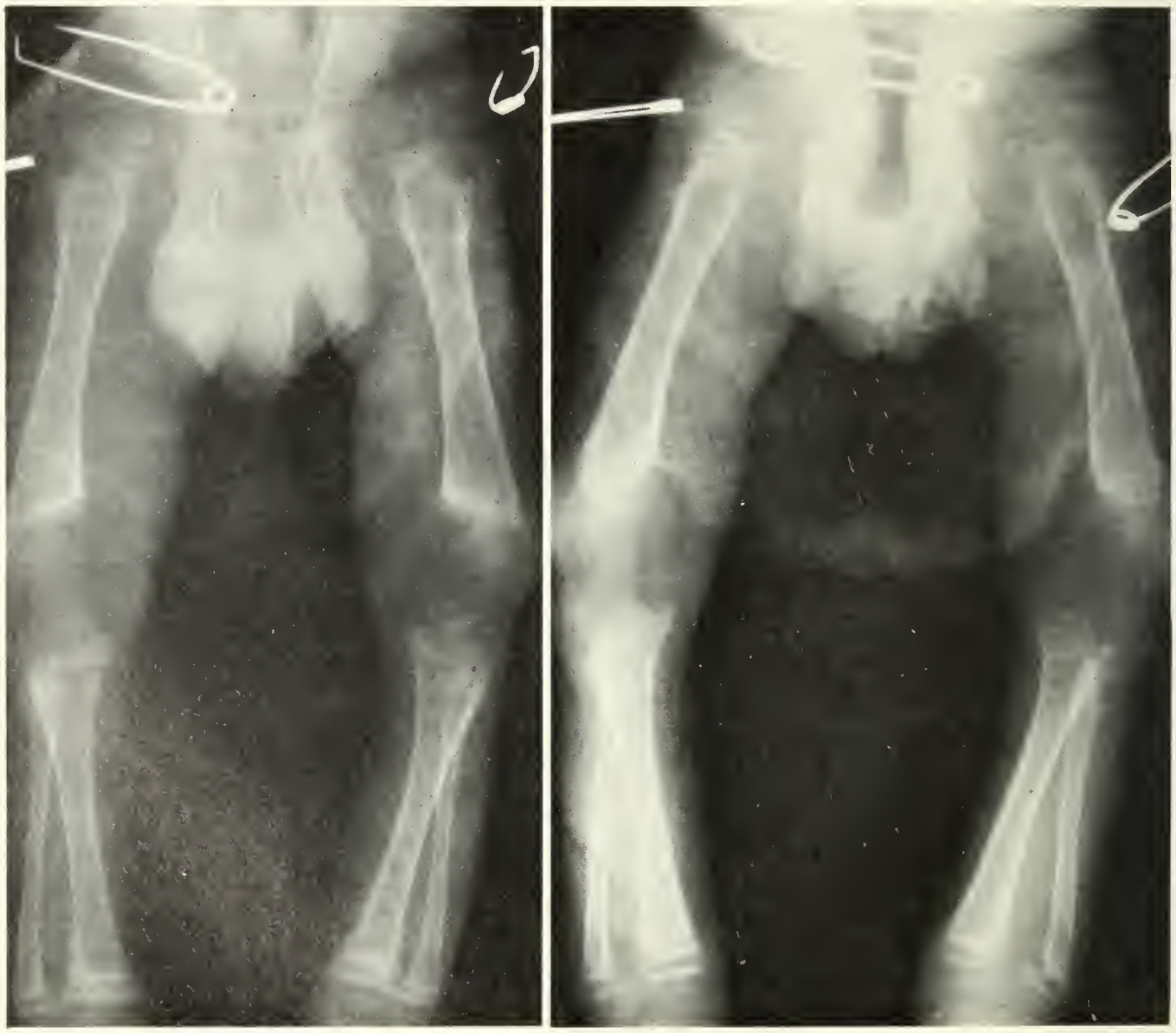

Figure 6.—Twin chimpanzees with rickets. Metaphyseal cupping and flaring, widened growth plates, periosteal new bone and cortical thinning are present. In contradistinction to humans, in chimpanzees similar changes develop in both epiphyses and metaphyses.

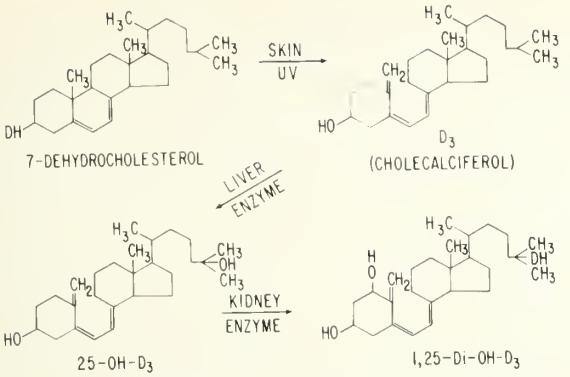

Figure 7.—The conversion of 7-dehydrocholesterol to its metabolites with vitamin D biological activity.

JERRY SCHNEIDER, MD:* I would like to begin with some comments about vitamin D and nutritional rickets. We should ask whether vitamin D is really a vitamin. I would like to suggest that it is not. It was named vitamin D because it was the fourth unidentified nutrient to be discovered.[1] Analysis of the structure (Figure 7) of the natural D vitamin, cholecalciferol, that we all make in our skin indicates that it is really a steroid and it is appropriate to think of it as such.

The history of vitamin D and rickets is fascinating.[1-4] Park's paper is very good. We do not know much more, from a clinical point of view today than he did 50 years ago.[2] Loomis has written two articles that deal with the history of vitamin D.[3,4] One in *Scientific American*[4] described the scientific arguments of investigators who thought rickets was a nutritional disease and those who thought it was environmental. Park felt that we should not think of rickets as a vitamin deficiency disease in the sense of beri beri and scurvy, but as an endocrine disease such as diabetes. Others have used thyroxin as an analogy. Cholecalciferol is produced in the skin just as thyroxin is produced in the thyroid. All of us have 7-dehydrocholesterol in our skin (Figure 7). Ultraviolet irradiation from the sun converts this in the skin to what is called vitamin D_3 or cholecalciferol. Only sunlight is needed to avoid rickets. Loomis considered rickets the first disease of air pollution.[3,4] Areas in which rickets first became prominent in Northern Europe were the areas in which soft coal was first used. The first clinical descriptions of rickets coincided very well with the introduction of soft coal.

Dr. Weller pointed out significant findings on x-ray films of two monkeys. Some pertinent studies were done at the turn of the century in London zoos. Animals that were fed a perfectly good diet in London zoos developed rickets, whereas their siblings, fed the exact diet in small zoos in nonindustrial areas of England did not. Loomis compared the distribution of skin pigment in various areas of the world with the availability of ultraviolet radiation from sunlight.[3,4] He proposed that lightly pigmented skin evolved in order to allow enough cholecalciferol production to prevent rickets. Some exceptions to the rule are easily explained. For instance, the Eskimos tend to have dark complexions, but live on a diet of fish which is rich in vitamin D. Fish are the only vertebrates that can make vitamin D without ultraviolet radiation.

It is humbling to read the history of cod liver oil. For many years leading physicians refused to believe that it had healing properties. Another interesting question is how people who lived in Northern Europe in areas without air pollution, but too cold to allow much exposure to sunlight in winter months, avoided rickets before widespread dietary supplementation with cod liver oil. The vitamin D that can be synthesized by a square centimeter of skin has been calculated, assuming the skin is very light in color so the ultraviolet light is not filtered out. A square centimeter of skin can make 18 units of vitamin D in three hours. Scandinavian mothers have known for hundreds of years that it is important to put their children outside each day for a few hours to get some fresh air and sunshine. These children are completely bundled on cold days, but their nice pink cheeks are exposed to the sunlight and you can calculate the square centimeters of skin exposed and find that in three hours about 400 units of vitamin D is produced. In the production of clinical rickets an absence of sunlight is a requirement. Linear growth of bone is also required to produce rickets. If a patient is very poorly nourished and not growing, rickets will not occur.

An excellent reference source on clinical rickets is the chapter by Harrison in Brennemann's *Practice of Pediatrics*.[5] It is relevant to the last two cases presented today to note what Harrison[5] wrote at least ten years ago:

> "Vitamin D deficiency may be apparent by 2 to 3 months of age particularly in prematurely born infants. The important finding at this stage is often hypocalcemia with only moderate reduction of serum phosphorus levels. Since the

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normal serum phosphorus concentration in the premature infant at this age is so high, a serum phosphorus level of 5 mg/100 ml may represent a relative hypophosphatemia."

This statement almost perfectly describes the third patient. Many physicians confronted with such an infant would feel that a serum phosphorus concentration of 5.2 mg per 100 ml was too high to permit a diagnosis of rickets since in a typical case of rickets the concentration would be under 4 mg per 100 ml. However, the normal serum phosphorus level in a 4-month-old infant is 6.4. In this infant, hypophosphatemia certainly was present.

In children with rickets there classically is a low serum concentration of phosphorus. The calcium level may be normal, or perhaps slightly low. In these children, however, there is very little calcium reserve. It is not possible in them for calcium to be mobilized from bones as quickly as in normal children; so their calcium balance is very precarious and they can easily be thrown into a situation in which the serum calcium rapidly decreases. This is often precipitated by infection. A few days of poor eating may cause the body to mobilize phosphorus precipitating some of the calcium and quickly lowering the serum calcium to a concentration that may cause tetany.

When I first saw the infant in the second case presented this morning, an article had just appeared in the *Journal of Pediatrics* by Lewis and co-workers.[6] They had specifically examined premature infants for rickets who were not given vitamin D. Their reasoning was that 400 units of the vitamin per quart of formula was only adequate if the infant actually took a quart of formula per day. Premature infants often take much less and, consequently, they get much less vitamin D. It has been known for many years that premature infants are especially susceptible to rickets. At one time doses quite a bit higher than 400 units a day were employed but I think most neonatologists now accept 400 units a day as sufficient. It is important that a premature infant actually get 400 units a day. Therefore it is wise to give 400 units a day of vitamin D as a supplement apart from the formula.

The treatment of rickets is somewhat controversial. The questions are how much vitamin D and how much calcium to give. Harrison[5] has been an advocate of a large push of vitamin D, amounting to 600,000 units of vitamin D administered as 100,000 units of D_2 orally every two hours for six doses. If nutritional rickets is present there should be a clinical response within one week and response noticeable on x-ray studies within two weeks. The rapid mobilization of calcium also protects against hypocalcemia. If no response is seen in two weeks, perhaps because of infection or steatorrhea, the dose is repeated. No more vitamin D is given for three months. Harrison has stated that he has never seen hypercalcemia following this form of treatment and that patients with vitamin D resistant rickets will not respond.[5] Other physicians never give this large a dose and prefer to give a few thousand units per day until they are sure of correction of the rickets. I like to employ large doses of vitamin D in a young infant with hypocalcemia tetany. It is very difficult in these infants to raise the calcium level quickly. A large dose of vitamin D may mobilize calcium rapidly and shorten the time in which parenteral calcium is needed.

The differential diagnosis of rickets may be extensive. If we consider the cases presented, there is little else but nutritional rickets that the infants in the last two cases could have had. We always think of vitamin D resistant rickets but rickets usually does not appear in these children until after 6 months of age, and they are normocalcemic. A point that might be helpful is that children with nutritional rickets tend to have a generalized aminoaciduria, whereas the vitamin D dependent type of rickets, which occurs as an autosomal recessive disorder, and the classic X-linked vitamin D resistant rickets do not. In children with the autosomal recessive form, rickets does not develop until 1 year of age and there tends to be a normal serum phosphorus concentration, while a low serum phosphorus level is the hallmark of a patient with the X-linked form.

One difficulty in understanding vitamin D metabolism is that there is no easy method of measuring vitamin D. Only tedious bioassays are available for this purpose. There are many questions that could be answered more easily if we could frequently measure vitamin D. For instance, why are premature infants more susceptible to rickets? Is it because they do not absorb vitamin D as well? Is it because of their small calcium reserve? Is it because they are not yet metabolizing vitamin D completely? These are questions to which we really do not have answers.

In recent years there has been a tremendous

increase in our understanding of vitamin D metabolism. This was initiated by the synthesis of highly radioactive vitamin D and its incubation in various systems. Most of the work has been done in rats and chicks. It was found first that the liver was able to add a hydroxyl group to vitamin D_3, forming 25-hydroxy-cholecalciferol (Figure 7). When this information appeared people became terribly excited because it appeared this might be the answer to vitamin D resistant rickets. Perhaps children with vitamin D resistant rickets lacked the liver enzyme which catalyzes this hydroxylation. This compound was given to patients with vitamin D resistant rickets. It was found that it was effective in vitamin D resistant rickets, but that the dosage required was much higher than the physiological amount. This compound was required in an equivalent dosage to vitamin D to get an equivalent response. These observations excluded the hypothesis. More recently it has been discovered that 25-hydroxy-cholecalciferol is further metabolized in the kidney to the product, 1, 25-dihydroxy-cholecalciferol. This dihydroxy form is extremely active both in stimulating the absorption of calcium from the intestine and in mobilizing calcium from bone. It too has been found not to be the answer to X-linked hypophosphatemic vitamin D-resistant rickets. These new compounds are of enormous theoretical interest. In coming years they are certain to be of clinical importance. Several publications have been included[8-12] in the references that provide detailed information on the metabolism of vitamin D.

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Pancreatic Insufficiency and the Role of Vitamin B_{12} Injections

Patients with pancreatic insufficiency, like patients with other forms of malabsorption, will require replacement therapy. . . . It is clear that patients with pancreatic insufficiency rarely have osteomalacia. Therefore, the requirement for calcium and vitamin D in patients with pancreatic insufficiency is less than in patients with primary malabsorption of the gut. . . . If you can give them the pancreatic enzyme, and they can take it, I would not worry about their vitamin B_{12} malabsorption because they should be absorbing B_{12} normally.

O. DHODANAND KOWLESSAR, MD, *Philadelphia*
Extracted from *Audio-Digest Family Practice* Vol. 24, No. 10, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Important Advances in Clinical Medicine

Epitomes of Progress—Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

The Current Status of Allergy Immunotherapy

ALTHOUGH immunotherapy for allergic disease is not new, only recently has the efficacy of this mode of therapy in certain allergic diseases been shown and we now have insight into the possible mechanisms of action.

Double-blind controlled studies comparing active allergenic extract and placebo have shown efficacy of ragweed and grass pollen injections in hay fever and bronchial asthma, while therapy for house dust allergy resulted in decreased bronchial sensitivity to the allergen, and improved clinical status in asthmatic children. The effect of treatment is dose-related but is limited by the allergen dose which can be tolerated safely. Patients with anaphylactic reactions to hymenoptera react less when restung than those who are untreated, although double blind studies have not been done. The current recommendation is for lifelong treatment, since several deaths have been reported after discontinuing injections even after three years of therapy.

Identification of IgE as the immunoglobulin with reaginic activity and the utilization of the leukocyte histamine release *in vitro* have shed light on the immunological and biological phenomena occurring with immunotherapy. It would appear that increased blocking antibody, decreased basophil sensitivity and decreased IgE antibody synthesis occur with treatment.

It should be stressed that allergen elimination whenever possible, and proper pharmacological therapy supplement immunotherapy for successful management of allergic patients, and the immunotherapy is not applicable in cases of food allergy.

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Poison Oak Desensitization

THE SKIN ERUPTION produced by the Rhus plants —poison oak, poison ivy and poison sumac—is an allergic contact dermatitis occurring in patients sensitized to the plant oleoresin. Highly sensitive patients may react to casual or inapparent contact, such as from burning leaves or by secondary transmittal from household pets or horses. Poison oak plants are widely distributed throughout the West and are difficult to eradicate. The disease is a serious problem for allergic persons working outdoors—such as foresters, rangers and telephone linesmen.

Desensitization by oral or parenteral administration of Rhus extracts has been used for many years, but the value of this form of prophylaxis has never been established fully. Individual reports of successful desensitization are difficult to accept, because natural loss of sensitivity through repeated contact ("hardening") or simple avoidance of contact with the plant could account for some of the apparent successes. Commercially-available extracts are sometimes inactive, and active extracts may induce serious reactions in highly sensitive persons.

Epstein and co-workers recently conducted a study of the effectiveness of desensitization using the purified allergen uroshiol extracted from poison oak leaves collected in California. The compound was administered orally to volunteers with high-grade sensitivity, and the effectiveness was determined by repeated titration-endpoint patch testing, using a double blind experimental design. The results were not dramatic, but in some patients there was significant reduction in sensitivity, which was dose-related. Some of the placebo-treated subjects showed decreased sensitivity, probably attributable to the repeated patch testing. Pruritus ani and skin rashes were observed in some instances. Attempts to inject urushiol intramuscularly were abandoned because of unacceptable inflammation at the injection sites.

The results of this study should encourage other investigators to pursue the search for a more effective and less toxic desensitizing procedure for this distressing condition. However, there is no evidence at present that currently available Rhus extracts can be recommended for desensitization.

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Viral Infections as Triggers of Asthmatic Attacks

MOST ASTHMATIC PATIENTS have attacks of asthma in association with respiratory infections. This phenomenon occurs in persons with intrinsic asthma, as well as in those patients with atopic allergy. Cultures of the respiratory secretions during such attacks generally fail to show specific pathogenic bacteria. There is a strong suggestion on clinical grounds that the respiratory infections most likely to exacerbate asthma are viral in cause. Several recent studies have helped to clarify the role of specific viruses as precipitating factors in asthma.

McIntosh and co-workers conducted a two-year study with 32 asthmatic children under age 5. The children lived in a residential treatment center, and most of them were atopic. It was found that 42 percent of their asthmatic attacks were associated with viral respiratory infections verified by cultures, in contrast to a lack of correlation with bacteria in their secretions. Respiratory syncytial virus infections almost always precipitated an attack of asthma, which was usually accompanied by bronchopneumonic infiltrates. Parainfluenza and coronavirus infections occurred frequently but less consistently exacerbated asthma, whereas adenovirus infections usually did not cause asthma unless the infection was especially severe. A single mild epidemic of influenza A_2/Hong Kong caused no wheezing in this population.

In a study by Minor and associates, older children and adults who were outpatients were studied. These patients were mostly nonatopic and were carefully selected for previous history of infection-provoked asthma. Rhinovirus infections usually triggered asthma when the infection was symptomatic, almost invariably when symptoms were severe. Influenza A and respiratory syncytial virus infections also provoked wheezing when infections were symptomatic, but adenovirus infections did not. Bacterial infections failed to trigger asthmatic attacks. This study showed further that primary viral respiratory infections did not produce a secondary bacterial component.

Viral respiratory infections are clearly capable of triggering attacks of asthma in patients of all ages, and they do so quite frequently. At least several viruses are asthmagenic, and the severity of the infection may be more important than the specific virus.

The mechanism is unknown, but viral-induced

hyperresponsiveness of the bronchi to endogenous mediators, hypersensitivity to viral antigens or mechanical irritation by direct invasion of the respiratory mucosa all have been postulated. Further studies may help to develop effective means of preventing transmission of respiratory viruses to patients with asthma through immunization or by other methods.

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Beclomethasone—An Inhaled Steroid for Bronchial Asthma

CORTICOSTEROIDS may be necessary in the management of patients with chronic asthma who do not respond to other modes of therapy. The principal mechanism of action is unknown, but the steroids are thought to act at least in part by enhancing the responsiveness of beta adrenergic receptors. Although they are effective in controlling asthma, serious side effects—particularly cushingoid features, pituitary and adrenal inhibition, and growth suppression in children—occur along with long-term use. Because of these limitations, aerosol therapy with topical doses was investigated. The initial studies with water soluble preparations, such as dexamethasone phosphate, did not show them to have any significant advantage over oral therapy. An aerosolized halogenated steroid ester, beclomethasone dipropionate, which is active in the respiratory tract, rapidly metabolized and has few systemic side effects, has been developed for use by steroid dependent patients with asthma.

Beclomethasone is 5,000 times more potent than hydrocortisone as a vasoconstrictor in the skin. Most of the inhaled drug is swallowed, and although efficiently absorbed, the small amount of steroid is rapidly inactivated. Adrenal suppression and growth inhibition are spared by the commonly recommended dose. Each inhalation contains 50 μg of steroid and the starting dose is two inhalations four times a day. Several reports indicate that in most steroid dependent patients with asthma, the oral steroid requirement can be substantially reduced while increasing pulmonary function and improving asthmatic symptom scores. In addition, there is a reduction in systemic effects while the patient is receiving beclomethasone.

When beclomethasone use is begun in a steroid dependent patient with asthma, orally given prednisone must be tapered very slowly and the patient observed for evidence of adrenal suppression.

Attendant with lowering of systemic steroids while using this aerosol, flares of eczema, allergic rhinitis and nasal polyps have been noted. Oral thrush has been seen in some patients, but there have been no reports of monilial lung infections. In those patients with asthma who are using this aerosol, short bursts of short-acting systemic steroids may be required during exacerbations of the illness. Use of beclomethasone is not indicated in status asthmaticus or in situations where steroids are not normally required, such as exercise-induced bronchospasm and infrequent asthma attacks.

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The Role of IPPB in Asthma

INTERMITTENT positive pressure breathing (IPPB) was introduced as a form of assisted ventilation for patients with respiratory failure. It was soon extended to the treatment of status asthmaticus and with the addition of bronchodilating drugs even to ambulatory patients with acute asthma. Despite widespread use, there has been insufficient documentation that this treatment modality is superior to bronchodilators administered subcutaneously or by hand-held nebulizers. Findings in some studies suggest that IPPB delivers a higher dose of drug to the affected site in the bronchi. However, others show insignificant difference in results on clinical improvement and pulmonary function tests whether a drug was delivered by IPPB, hand nebulizer or a nebulizer attached to an electric air compressor. Although there may be other beneficial effects, such as inducing increase in tidal volume and improvement of distribution

of ventilation, these are likely to be as transient as the duration of each treatment.

Recently, a number of articles and editorials has condemned the indiscriminate use of IPPB in patients not dependent on assisted ventilation. Attention is called to inherent risks such as air trapping, infections, pneumothorax, arterial hypoxia, arrhythmia and psychologic dependency, as well as the expense of the instruments. It is now thought that IPPB has a very limited role in the therapy of acute and chronic asthma.

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Prophylaxis of Allergy

THERE HAS BEEN controversy over prophylactic measures for allergy since Glaser described a pronounced diminution in the expected incidence of atopy when he managed the siblings of his allergic patients with a prophylactic dietary regimen. In essence his treatment of families with a high incidence of allergic disease consisted of having the expectant mother avoid eggs and cow's milk before the baby's birth, and having the infant avoid milk and dairy products, chicken, egg, and wheat for the first nine months of life. Halpern could not confirm Glaser's findings in a study which included breast feeding or use of soy-based formulas; he observed no decrease in the incidence of allergic disease. However, the two studies are not directly comparable.

In a prospective study of serum IgE levels during the first year of life, Orgel and Hamburger were able to predict which babies had an increased risk of allergy. Their earlier work indicated some prophylactic value to breast feeding in infants of allergic parents. They are presently studying the effect of dietary and environmental prophylaxis on serum IgE levels as well as on the development of allergy. Preliminary results indicate that prophylaxis does not prevent the early elevation of serum IgE levels that has been found in infants with atopic disease but may prevent the development of symptoms.

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The Role of Eosinophils in Allergy

THE ASSOCIATION between increased numbers of eosinophils in blood and reacting tissues of allergic reactions has been known for decades. In the past few years the role of these eosinophils has become clearer.

Many factors cause eosinophil chemotaxis. These include complement-derived products, C5a and C3a, and active site plasma factors, kallikrein or plasminogen activator. The most potent chemotactic factor is Eosinophil Chemotactic Factor of Anaphylaxis (ECF-A) which is preformed in human basophils and mast cells and is released from these cells by IgE antibody-antigen allergic reactions.

Eosinophils share with neutrophils the ability to phagocytize particles including immune complexes. The eosinophil granules contain many of the hydrolytic enzymes present in neutrophils as well as additional enzymes peroxidase, phospholipase B and arylsulfatase. The last of these enzymes inactivates one of the important chemical mediators of asthma, Slow Reacting Substance of Anaphylaxis (SRS-A). Eosinophil histaminase inactivates histamine in the allergic reaction. High concentrations of ECF-A or phagocytosis cause the eosinophils to release these enzymes during an allergic reaction.

Specific allergens have been shown to cause eosinophils from allergic persons to release eosinophil-derived inhibitor (EDI) which is thought to be prostaglandins E_1 and E_2. These inhibit the release of histamine and probably SRS-A from human mast cells and basophils. This inhibition, which is similar to the action of catecholamines, is due to the increase in intracellular levels of cyclic-adenosine monophosphate (AMP).

From this information it appears that eosinophils help to regulate or possibly terminate an allergic

reaction. This is done through inhibiting allergic mediator release as well as inactivating these chemical mediators.

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The Early Detection of Childhood Asthma by History

THE TERM ASTHMA may refer to a single episode of wheezing, coughing and difficult breathing due to obstruction of the airway by bronchospasm, mucous membrane swelling and mucus secretions. It is also a term for a constitutional characteristic of some allergic persons in whom allergy periodically presents in this way. These people are referred to as "asthmatic."

Most of such persons consider themselves free of respiratory problems except for an occasional attack of asthma. Closer examination of their history, however, often shows evidence of a minor degree of respiratory tract allergy which is present much or even most of the time.

Detection of such minor symptoms often is the key which permits recognition of the probable asthmatic nature of what otherwise might be diagnosed as bronchitis, pneumonia, bronchopneumonia, bronchiolitis or even croup.

The minor symptoms include coughing at night, coughing or occasional wheezing on exertion, an above average amount of sneezing and itching, postnasal drainage and rubbing of the nose. Although the latter symptoms are not directly linked with asthma, they are reliable signs of allergy in the upper airway which may signal accompanying allergy in the lower airway—that is, asthma.

Coughing at night (even though it may not awaken the patient) and coughing, dyspnea or wheezing on exertion are even more often signals of an underlying respiratory allergy. Early search for these clues in a patient's history is important since one may then proceed to look for their causes in order to prevent further episodes of asthma which will otherwise occur. It also puts into focus the noncontagious nature of the patient's disorder and explains why dependence on antimicrobial therapy may be unsatisfactory.

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Nasal Polyps and Allergy

ON TRANSNASAL EXAMINATION of the nose, nasal polyps are seen as grey, pearly-white excrescences. Occasionally they may not be seen anteriorly and may be viewed only on nasal-pharyngeal examination. Polyps are not true neoplasms. Histologically they are lined with columnar epithelium and contain the same elements as nasal mucosa. There is a pronounced variability in content of edema fluid and eosinophils. The pathogenesis of polyps is not clear. They are associated with allergic rhintis, infectious sinusitis, cystic fibrosis and aspirin sensitivity—the last usually associated with bronchial asthma.

Although eosinophilia is a hallmark of atopic disease, it is quite variable in polyps. In fact, it does not distinguish the atopic from the nonatopic state. Intense eosinophilia may be seen in an aspirin-sensitive, severe nonatopic asthmatic, while cosinophils may be sparse in polyps from a young, moderately allergic patient. However, those from atopic patients do contain large amounts (10 to 40 percent) of immunoglobulin E producing cells not seen in nonatopic patients.

Treatment is symptomatic and is designed to improve the nasal airway and prevent occlusion of the ostia of the maxillary sinuses. Chronic maxillary sinusitis is not an infrequent accompaniment of nasal polyposis. Dexamethasone, self administered by intranasal spray, will produce considerable reduction in polyp size—particularly in small polyps. If this treatment is not successful, surgical intervention is necessary but should be undertaken with the knowledge that polyps frequently recur.

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Adversely Reacting Drugs in Aspirin Sensitive Patients with Asthma

ASPIRIN INTOLERANCE in patients with asthma has been well documented. The reported prevalence of wheezing after the ingestion of aspirin in asthmatic patients has ranged from 2 to 20 percent. Results of a recent study in children with chronic asthma and no history of aspirin intolerance showed that 28 percent had a significant decrease in pulmonary function following aspirin challenge.

Persons who have aspirin intolerance may have adverse reactions to other drugs. Indomethacin, the anthranillic acid derivatives including mefenamic acid and flufenamic acid, and new nonsteroid antiinflammatory drugs such as ibuprofen, naproxin and tolmetin sodium caused bronchial constriction in some aspirin sensitive patients with asthma. Tartrazine, a Food and Drug Administration approved dye known as Yellow #5, has been reported to precipitate symptoms in some of these persons. Tartrazine is widely used as a food coloring to produce yellow, orange and green colors. It is used to color foods, beverages and tablet medications.

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The Allergy Physician's Assistant (APA) Training Program in California

WITH THE AID of a recently completed four-year United States Public Health Service grant, the allergy physician's assistant has emerged as a licensed professional in California. The program created a demand by allergists for skilled assistants and resulted in a valuable new type of professional, according to a recently published paper.

Allergy physician's assistants (APA) are knowledgeable in immunology, environmental studies (including botany and mycology), history taking, limited physical examination, preparation of allergen extracts, skin testing, environmental home studies, allergy treatments and office management.

Licensed graduates of the program are proving their value as a direct benefit to patients and physicians by helping physicians to give more quality time to the patient. They can provide closer follow-up, and supplement comprehensive care at lower cost. It has been noted that immunotherapy, especially in children, can often be avoided by expert environmental investigation and follow-up which results in the elimination of offending allergens.

The present APA program includes four semesters (six quarters) of academic and clinical study followed by a 12-week externship in a clinic or office practice. The program is a joint project of the University of California, San Diego, School of Medicine, and the University of San Diego Hahn School of Nursing and Allied Health Science. Successful graduates may be licensed in the state of California and may be employed by Boarded or Board eligible allergists.

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State of California, Department of Consumer Affairs, Board of Medical Quality Assurance, Physician's Assistant Examining Committee of the Division of Allied Health Professions: Rules and Regulations, Chapter 13, Title 16 of the California Administrative Code

The Effect of Childhood Asthma on Growth

IMPAIRMENT of the normal growth pattern is not unusual in children with bronchial asthma. This is related to both the severity of asthma and the dosage of corticosteroid that may be required to control the disease. Williams has shown that asthmatic children with barrel chest deformities had the most significant reduction in height and weight compared with age-matched normal controls. Furthermore, Falliers reported that 36 percent of asthmatic children in hospital who never received steroids were two standard deviations or more below predicted height. Poor growth in these children could be related to chronic hypoxemia. Improvement in growth and development follows resolution of persistent asthma.

It has been shown that prednisone in as little as 4 mg per square meter of body area in a daily dose can stunt growth. An alternate day dose of 18 mg

of prednisone, while producing fewer side effects, does suppress growth. Furthermore, alternate day therapy in low dose, while not growth suppressive, does not allow catch up growth to occur.

When possible prednisone should be used on an alternate day schedule at the lowest dose which can control the disease. Under these circumstances normal growth may occur. It remains to be seen whether the newer inhaled steroids such as beclomethasone may be of further aid in restoring normal growth, since they appear to be effective in controlling asthma without significant systemic effects.

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EDITORIALS

A BICENTENNIAL EDITORIAL

The Dollars for Health

QUITE SIMPLY, the number of dollars available for health is and will be far less than what can legitimately be spent, whether in research, education or health care services. As time goes on this gap between what could be used and what will be available will increase. America, now entering its third century, has already found that one of its major problems is how to deal with rapidly rising and seemingly uncontainable costs in the field of health. Expenditures for health have now reached 8.3 percent of the gross national product. It is clear that sooner or later there will have to be some sort of ceiling on the dollars spent for health, and that within this limitation, not only services, but research, education and medical progress will all have to share the available dollars.

As might be expected there is beginning to be some study of the subject. Some of the causes of rising costs are obvious, some are not. It has been observed that the laws of the market place which tend to control prices and costs do not seem to apply in health. A recent study[1] commissioned by the government and carried out by a nongovernmental research institute, found that a multitude of forces, each reinforcing the other, has pushed the health care system into ever greater emphasis on costly secondary and tertiary care, to the neglect of other levels of care which might be less expensive. The cost of labor and supplies has increased enormously and the price of inflation is added on. But there has been relatively little study of the dollars health care saves by preventing, curing or restoring productivity or, on the other hand, of the dollars it costs to maintain the chronic disability that occurs when restoration of health and productivity has been incomplete—and what, if any, might be the trade off.

But there are other strong but less obvious forces at work. For instance, conflicts of interest of various kinds pervade the field of health and these cannot help but affect costs. Patients and families have one view of expenditures when illness is serious, but the public or whoever foots the bill may have another. Even the patient or the family may have a different view when confronted with the bill. And public cost consciousness can conflict with public compassion, as in the End Stage Renal Disease program for example. Providers of care, especially physicians, find conflicts between what a patient really needs and what it takes to satisfy public accountability—utilization controls, quality assurance and defense measures in case of future litigation. And there are costly conflicts of interest within government itself. So far the federal government has been loath to apply the same cost controls to federal health care programs that it does to programs in the private sector. It seems likely that in no other field are there so many genuine conflicts of interest impinging upon costs, and mostly adversely.

Then there is a curious irrationality about health and health care. People are not always as concerned as we like to think they are. A surprising number believe "it won't happen to me" and take irrational risks. Others are unduly fearful. We know that a large number of patients do not follow their physician's advice or take their prescribed medicine even though they sought the advice and bought the medicine. Everyone knows that smoking and too much alcohol are bad for people, yet indulgence in both continues to be widespread in spite of all out efforts in education and control. It is clear that the costs of health care and the dollars for health cannot be separated from human behavior and that rational thought may not always prevail.

Given the cost problems, the conflicts of interest, the inherent irrationalities—not to mention imperfections in the science and art of medicine—what is to be done? Certainly something more than the ad hoc stop gap measures of today will be needed. Perhaps it is already time for a new approach. It is suggested that many of the dollars now being spent for health are not producing that much health. Would it not be worthwhile to reassess the assumptions upon which all health expenditures are based, whether in patient care, administration, education or research, and see what kind of data or experience supports them? Have not many programs and services been carried to the point of diminishing returns for the dollars being spent? And to what extent is the

friction in the system—and the cost—being increased by attempts to impose regulations and controls upon it, and is this worth the cost? It seems certain that many dollars now being spent for health could either be saved or spent more productively for health if questions such as these were asked and answered. And this is something that can be done now.

In the longer range it will be necessary to face up to the ever growing disparity between health resources and burgeoning needs. Judgmental decisions involving personal goals, societal goals and contemporary ethics will need to be made at all levels of health care. These will involve doctors, patients, consumers, administrators and the public. It will be necessary to develop the means by which a broadly based consensus can be achieved at all levels of health care on where and for what the relatively limited dollars available in this field will be spent, be they public or private dollars. It is clear that physicians will be involved in all of this. Their knowledge of what constitutes health and its disorders, their direct experience with patients and their more recent experience with the problems created as well as solved by governmental and other interventions will be essential. Their advice should be sought and listened to and they should take part in the decisions at every level.

It is not too soon to begin to get some new and more realistic approaches to all of this into place, so that the dollars for health care can both be conserved and used more efficiently and effectively.

—MSMW

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Venous Thrombosis

From time to time, new technology provides both the impetus and the means for a dramatic gain in our ability to cope with a serious disease. So it is with venous thromboembolism. The recent renewal of interest in this familiar problem can be traced largely to the development of improved diagnostic methods. Sensitive and objective techniques now available have led to an appreciation of the prevalence of thromboembolism complicating the postoperative state and occurring in nonoperative patients; they have provided increased understanding of the natural history of the disorder; they have underscored the insensitivity and unreliability of diagnosis when based solely on clinical criteria, and they have afforded investigators a means of generating solid data in studies of prevention or treatment.

Radiographic phlebography and scanning of the lower limbs for uptake of labeled fibrinogen have been particularly influential. The former procedure is at present regarded as the ultimate standard for showing the presence of venous thrombosis in the lower extremities of living patients, when carried out by modern techniques.[1,2] Although invasive and not without morbidity, it is superior even to routine autopsy in its sensitivity. The latter method, available for general use now that ^{125}I-labeled fibrinogen is commercially distributed in the United States, has been of greatest value in clinical investigation, where it has provided objective data on occurrence rates. Its most important contribution so far has probably been the trial and proof of low dose heparin as a prophylactic agent in postoperative patients.[3,4] Labeled fibrinogen scanning will undoubtedly continue to be valuable as a surveillance method, but its greater application in clinical practice may prove to be as a diagnostic measure in patients in whom a preformed venous thrombus is suspected to exist, even though the technique is less sensitive with established thrombi than when employed as a screening procedure and administered in advance in high risk cases.

Recent noninvasive additions to the diagnostic armamentarium, such as plethysmographic techniques,[5-7] appear to achieve their highest degree of accuracy in detection of major thrombi in the femoral and iliac veins, which are probably the source of most serious pulmonary emboli. Therefore, they are promising methods for confirmation of a clinical impression based on swelling and tenderness in the thigh. Their advocates claim that, if they give negative findings, they can provide comforting assurance of a minimal hazard of major pulmonary embolism.[8] However, these techniques are essentially blind to thrombi in the calves, and this point must be kept in mind in considering their clinical applicability. The litera-

ture on calf thrombi is inconclusive with regard to their ultimate potential for harm, and there is controversy about the relative necessity for their diagnosis, and for their treatment once they are found. That thrombi confined to the calf can lead to embolization is certain. The points at issue relate to frequency, to severity and to how often this occurs without preliminary extension into the thigh.[9] Having no certain guidelines in respect to these important questions, clinicians should at least be aware of the limitations of noninvasive methods.

Careful studies employing objective diagnostic techniques have considered the question of preventing venous thromboembolism in high risk patients, and several modes of prophylaxis have now been shown to be effective in specific patient groups. It is established, for example, that in patients undergoing elective general surgical operations, small subcutaneous doses of heparin will prevent postoperative venous thrombosis and pulmonary embolism, including fatal pulmonary embolism.[4] The frequency of bleeding complications, while increased, is not great and, excepting patients with an underlying predisposition to hemorrhage, is an acceptable price to pay for freedom from thromboembolism. Unfortunately, low dose heparin appears to be ineffective in patients with fractures of the hip and in those in whom elective surgical operations on the hip are done,[10,11] and a reasonable extrapolation from this experience would require one to employ a more potent form of prophylaxis in other very high risk patients, such as those with a history of previous thromboembolic disease.

Oral anticoagulants (that is, warfarin and its congeners) have been found effective in these high risk situations. An enormous literature exists in support of the ability of vitamin K antagonists to prevent venous thromboembolism,[12,13] and there can be no doubt that they are effective in conditions in which low dose heparin is insufficient. However, an increase in bleeding complications with warfarin has limited acceptance of this mode of prophylaxis in postoperative patients, despite proof of the efficacy of the drug. For patients whose susceptibility to bleeding does not create a hazard in the use of warfarin, it is probably the antithrombotic agent of choice.

Drugs whose antithrombotic effect results from their ability to alter platelet function have been evaluated as prophylactic agents, and there is evidence for their success in selected instances.[12] Dextran has a large literature to confirm its effectiveness, but frequent side effects such as pulmonary edema and allergic reactions have prevented it from wide adoption as a routine prophylactic drug. Support for the use of aspirin, hydroxychloroquine and other antiplatelet agents is also to be found, but the data are incomplete and further evaluation is necessary.

Although early ambulation may be adequate for prevention of venous thrombosis in nonoperative patients, it is inadequate in surgical cases, and elastic stockings and elevation of the legs have also been found insufficient to prevent deep vein thrombosis in high risk patients.[14,15] Other physical measures, however, appear more promising. Electrical stimulation of the calf muscles and compression of the calves by inflatable boots have been shown to reduce venous thrombosis. Their efficacy has been documented in general surgical patients,[16] in patients undergoing open urological operations[17] and in neurosurgical patients,[18] the last being particularly of interest because they are not candidates for the use of antithrombotic drugs. Patients at very high risk may not receive adequate protection from these techniques,[19] and the task at hand is to define the groups in which their use is appropriate and in which they offer an alternative to pharmacologic agents.

The availability of a number of effective preventive techniques offers a physician the opportunity to prevent a complication that is frequent, often disabling and occasionally lethal. One may expect that the wider use of antithrombotic prophylaxis will characterize good practice in the coming years.

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PSRO — Update 1976

It is now well over three years since PL 92-603 with its mandate for Professional Standards Review Organizations (PSRO's) became law and it is time for another commentary in these columns. This is an exceedingly complex law and progress in implementation has been slow, partly because the funding has been at little more than a subsistence level, and perhaps partly due to some wisdom and restraint on the part of those responsible for its implementation.

There are now 87 PSRO's with conditional contracts, 33 more with planning contracts and 83 of the 203 designated PSRO areas still have no contracts. PL 94-182 extended the time professional organizations would have priority in establishing PSRO's from 1 January 1976 to 1 January 1978—except where the membership association representing the largest number of doctors of medicine in an area has adopted a formal policy of opposition to PSRO's, or where a professional organization proposed by the Secretary of the Department of Health, Education and Welfare (DHEW) for designation as a PSRO has been voted down. So far this has occurred infrequently. It now appears that further progress depends as much on the availability of the necessary funding as on anything else.

The accomplishments to date make possible some reflections on specific problems as these have emerged and evolved. The relationship between cost control and quality assurance—the apparently conflicting stated aims of the law—has not yet been defined. However, one senses a growing realization that one is not acceptable without the other and that somehow a reasonable accommodation of the two must be achieved. It remains to be seen how this generic problem will be solved.

With regard to the less generic and more specific, the bureaucratic infighting between the "H" and "W" within DHEW seems to be less obvious than it was, and an end run by "W" on utilization review regulations was restrained by the courts after suit was brought by the American Medical Association. Presumably new and more workable utilization review regulations will be forthcoming. Also in the crucible is the relationship of the national PSRO administration to local PSRO's, particularly what is the legal authority of the PSRO "letters of transmittal" and what "due process" is available to a local PSRO in the event of disagreement. These issues are fundamental and pertain to the rights of a local PSRO as a party to a contract with the federal government. Another problem, under discussion and also unresolved, is the collection, use, storage, "ownership" and confidentiality of the patient care data to be collected by the local PSRO's. Again the issues are fundamental and involve rights to privacy, the rights and responsibilities of practitioners to exercise their judgment and expertise (and the expectations of their patients and consumers of health care that they will do so), and the right and responsibility of government to monitor public funds and to achieve what it perceives to be the nation's goals.

In any commentary on the PSRO law it is also well to remember that some basic assumptions of the law are still just that—assumptions. It is assumed but has not yet been really shown (1) that systematic peer review can actually assure quality of care, (2) that by eliminating excessive utilization, costs can be significantly reduced or (3) that the administrative paraphernalia that is to be set up will be cost—or quality—effective. Nor should it be forgotten that the technology that will be needed to accomplish the stated purposes of the law has hardly been developed.

So there is much that is unresolved and much that remains to be seen. As well as being based on untested assumptions and requiring technology which has yet to be developed, this complex law addresses many sensitive issues that strike at some

fundamental aspects of the American way of doing things. How things work out will indeed be a test of how Americans do things. It is to be hoped that the aims of the law can be achieved. Quality assurance and cost containment in medical care are goals shared by all concerned. Ideally there can be a true partnership between government and the private sector. Ideally the problems and conflicts can be resolved by persons of good will, without undue use of force on the one hand or resort to the courts on the other. There is much at stake in this largely uncharted area of professional and public interaction. So far the program is apparently being implemented slowly and on the whole wisely—and this is about all that can be expected at this time.

—MSMW

Rickets

THAT A specialty conference on rickets (such as appears elsewhere in this issue) should command interest in 1976 is in itself a matter worthy of comment. In the 1950's it was generally held that everything worth knowing about rickets had been learned. An ancient disease which had become a major affliction of infants and children in the industrial cities of northern Europe and the United States during the 19th and early 20th centuries had at last been conquered.[1] The consequences of rickets in childhood were not only the hypocalcemic tetany and the visible deformities of head, chest, spine and legs of the severely rachitic child, but also the hidden deformity of the pelvis which in the female was a major cause of dystocia and almost certainly of maternal and infant mortality and morbidity.

Following development of an animal model for rickets in 1918 there followed quickly the identification of an antirachitic factor in cod liver oil separate from the already known vitamin A in this odoriferous and rather unpleasant tasting folk remedy for rickets. The relationship of ultraviolet energy to vitamin D was also soon learned, leading to the development of a laboratory process for production of concentrated preparations of vitamin D by irradiation of ergosterol—a plant sterol—or 7-dehydrocholesterol—the sterol from which the natural vitamin D is produced in the skin of man—by exposure to short wave ultraviolet radiation. These concentrated preparations of vitamin D were inexpensive to prepare and could be added without difficulty to evaporated milk, homogenized pasteurized milk or the special infant feeds based on cow's milk whey. Since this fortification of cow's milk with vitamin D coincided with the trend away from breast feeding the result was that most infants automatically received enough vitamin D without the necessity for the mother to add vitamin preparations or to attempt to expose the infant's skin to sunshine, which would not be helpful anyway in winter months in northern latitudes. The importance of skin exposure to sunshine as a source of vitamin D is emphasized by the low vitamin D content of human milk so that breast-fed infants not given vitamin D are at risk for rickets—as illustrated by Case 3 presented in this month's specialty conference.

By 1950, vitamin D deficiency rickets had become an uncommon disease instead of an everyday problem. At that time it seemed that further research on vitamin D might provide theoretical information of interest but was not likely to have practical application in the treatment of patients. Research did continue, however, because of the desire to understand the physiologic basis of the action of this highly potent agent of which only a few micrograms a day were sufficient to prevent rickets.

Investigators of the physiology of vitamin D took advantage of new techniques for the study of calcium homeostasis. One was the use of isotopic calcium, which simplified investigation of calcium absorption from the intestine[2] and made possible the study of calcium turnover in the skeleton, so called calcium kinetics. Of great value was the adaptation to the study of intestinal calcium transport of a method devised by gastrointestinal physiologists for examining intestinal absorption of organic solutes such as glucose and amino acids. This was the everted intestinal preparation, an *in vitro* system that could be used for measuring net mucosal to serosal transport of calcium.[3,4]

It was quickly found that such transport was much greater in preparations from rats treated with vitamin D than from vitamin D depleted animals. It was also learned that vitamin D had to be given to the animal at least several hours before the intestine was removed for the *in vitro* study even when very large doses of vitamin D were fed. The basis of this lag period then became the subject of intensive study. Two theories were

developed: (1) that the vitamin had to be transformed metabolically into an active principle by tissues other than the intestine and (2) that vitamin D acted in the intestinal mucosal cells to induce synthesis of a protein or proteins which functioned to facilitate transport of calcium and of phosphate. Both theories proved to be correct. Evidence was developed that vitamin D did activate DNA-mediated mRNA synthesis and induce the synthesis of at least one specific intestinal cell protein characterized by its ability to complex calcium and called calcium binding protein (CABP).[5]

At the same time, the studies by DeLuca and his colleagues indicated that vitamin D was hydroxylated in the liver to 25-OH vitamin D which stimulated calcium transport by the everted intestinal preparation with a shorter lag period than did vitamin D.[6] Results of studies by Norman and also Kodicek[7] indicated, however, that the compound which complexed with the nuclear chromatin of the intestinal mucosal cell was not 25-OH vitamin D. A further metabolite of 25-OH vitamin D (1,25-di OH vitamin D) was discovered that is the presumed active vitamin D hormone.[8] The extraordinarily interesting fact about this compound is that the kidney is the only site of its production. There is thus a complex cycle of vitamin D metabolism with an initial hydroxylation by a liver microsomal system and a second hydroxylation by a kidney mitochondrial system.

The latter system is controlled by a feedback mechanism that adjusts the production of the vitamin D hormone to the concentrations of calcium and phosphate in body fluids. The formation of 1,25-di OH vitamin D is stimulated by parathyroid hormone and by a low concentration of inorganic phosphate. Calcium deficiency resulting from a low calcium diet stimulates parathyroid hormone output which in turn increases the formation of 1,25-di OH vitamin D which operates to increase the efficiency of calcium absorption. Hypophosphatemia also stimulates 1,25-di OH vitamin D production. This compound functions to increase both phosphate transport in the intestine and also renal tubular reabsorption of phosphate as an adaptive function. The interrelationship between parathyroid hormone and vitamin D is complex in that not only is parathyroid hormone needed for adequate formation of 1,25-di OH vitamin D but vitamin D is required for the full action of parathyroid hormone. Hypocalcemia with convulsions is, therefore, an important early manifestation of vitamin D deficiency (Cases 2 and 3 in the specialty conference).

By chance the elucidation of the vitamin D cycle coincided with the development of new thoughts about the treatment of chronic progressive renal disease including not only diet but aggressive measures to replace the defective kidney function such as dialysis and renal transplant. It was now possible to understand the calcium malabsorption and secondary hyperparathyroidism of kidney failure in terms of deficiency of 1,25-di OH vitamin D resulting from the reduced metabolic mass of kidney tissue and also the hyperphosphatemia secondary to glomerular insufficiency. With this understanding have come better methods for preventing this secondary hyperparathyroidism and the consequent skeletal demineralization and painful deformity which incapacitated patients with severe kidney insufficiency.

Vitamin D deficiency rickets is an uncommon problem today but forms of rickets are encountered that are not prevented by administering ordinary amounts of vitamin D. These vitamin D resistant varieties of rickets can now be classified and treated more effectively by virtue of better understanding of the metabolism and mechanism of action of vitamin D.[9] The hypocalcemia and rickets of infants with neonatal hepatitis or chronic obstructive jaundice is at least in part due to failure of 25-hydroxylation of vitamin D by the liver, which is a necessary step in the formation of 1,25-di OH vitamin D. Treatment of such patients with 25-OH vitamin D is effective.

The rickets and osteomalacia sometimes seen in patients with seizure disorders who are receiving treatment with anticonvulsant drugs[10] are possibly due to accelerated vitamin D metabolism and inactivation by glycuronidation, resulting from induction of hepatic enzyme activity by such drugs as phenobarbital and phenytoin. Study of this problem has been made possible by methods for determining the 25-OH vitamin D level in the serum based on the binding of this compound by receptors in kidney cytosol or binding proteins in rat serum. Although serum 25-OH vitamin D concentrations are reduced by treatment with anticonvulsant drugs, this may not be the sole action of these drugs and there is some evidence of a direct effect on calcium transport by the intestine. Because of the large numbers of children and adults receiving anticonvulsant drugs it is important to study this problem further.

There are forms of rickets, so-called vitamin D dependent rickets or where there is an increased requirement of vitamin D, that are the result of an inborn error of metabolism of vitamin D which may be a defect in the control of the 1-hydroxylation system in the kidney. The patient in Case 1, in whom more than the usual amount of vitamin D apparently was required to prevent rickets but in whom rickets healed after administration of 10,000 units of vitamin D per day, may represent a mild variant of this metabolic disorder. The family history supports a genetic basis for this problem.

It has been disappointing but not surprising to discover that the most common variety of rickets that is not preventable by vitamin D administration—that is, primary hypophosphatemic rickets—cannot be ascribed to a defect in the vitamin D cycle. The mechanism remains a matter of argument and various theories have been proposed, such as absence of a renal tubular transport system for phosphate other than that controlled by parathyroid hormone,[11] hyperresponsiveness to parathyroid hormone in physiologic concentration with inhibition of phosphate transport[12] and target cell refractoriness to 1,25-di OH vitamin D resulting in deficiency of calcium and phosphate absorption by the intestine and impaired tubular reabsorption of phosphate.[13] An even more speculative possibility has also been considered: that there may be a circulating humoral factor other than parathyroid hormone that inhibits tubular reabsorption of phosphate.[14] There is genetic heterogeneity of primary hypophosphatemia since a phenotypically identical disorder has been found in kindreds in whom the inheritance is through a dominant gene on the X-chromosome, an autosomal dominant gene and an autosomal recessive gene. Possibly there is heterogeneity of the physiologic defect also. Certainly there are pronounced differences among patients in the severity of the process which cannot be entirely explained by X-linked inheritance and the Lyons hypothesis. Despite differences of opinion concerning the physiologic defect there is agreement that megadoses of vitamin D are not curative and can be nephrotoxic. Treatment has therefore been altered to depend more on high phosphate intake in the form of a buffered solution of sodium and potassium phosphates to raise serum phosphate, with only enough vitamin D or dihydrotachysterol to maintain adequate calcium absorption and block parathyroid hormone secretion.

The history of rickets research should remind us—and such reminders may be necessary—that physiologic and biochemical research directed at understanding as completely as possible both the normal and the altered physiologic processes of disease provides not only satisfaction to scientists but benefits to people generally in the form of more effective prevention and treatment of disease.

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CASE REPORTS

Refer to: Schurman DJ, Aptekar RG, Burton DS: Infection in total knee joint replacement, secondary to tooth abscess. West J Med 125:226-227, Sep 1976

Infection in Total Knee Joint Replacement, Secondary to Tooth Abscess

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ALTHOUGH DELAYED INFECTION in total joint replacement is common, the cause of it has remained controversial. Charnley[1-4] maintains that delayed infections are not due to hematogenous infection from other sources of sepsis, but are the result of organisms introduced at the time of operation. Others maintain that patients in whom total joint replacement has been carried out are at risk from hematogenous infections which may occur elsewhere in the body.

In the case described here, bilateral knee infections occurred simultaneously in a patient a year and a half after hinge total joint replacement in both knees as a result of hematogenous spread from a persistent tooth abscess.

Report of a Case

A 61-year-old woman with rheumatoid arthritis and in whom there had been bilateral knee replacements entered Stanford University Medical Center in May 1975 with pain and swelling in both knees. Before this, in September and October of 1973, bilateral total knee replacements had been carried out utilizing the Guepar hinge, and cephalosporin prophylactic antibiotics had been given intravenously for four days at each operation. Before the knee replacement procedures, she had bilateral knee flexion contractures of 80 degrees, and was confined to a wheel chair with continuous pain. The postoperative course was unremarkable, with an unusually good functional result, no pain and more than 120 degrees of motion in each knee; the patient was able to walk unlimited distances using a single cane part time.

In March 1975 pain and drainage developed in right lower incisor tooth. Treatments were begun by her dentist in an effort to save the tooth, and incision, drainage and root canal work were carried out. At this time, osteomyelitis of the mandible about this tooth was seen on an x-ray study, and the patient suffered from intermittent fever. A regimen of four tablets of tetracycline per day for five days was begun. Some weeks later, and five days before admission to hospital, there was considerable pain in the tooth, and a drainage procedure was carried out by her dentist. The following day pain developed associated with swelling and inflammation of the right knee. During the next four days, the pain and swelling increased and the overlying skin became erythematous. On the day of admission, pain in her left knee developed.

On physical examination, a temperature of 38.2°C (101.1°F) was noted. Both knees were swollen and painful, with motions limited to less than 30 degrees. Results of laboratory tests included a leukocyte count of 12,600 and a sedimentation rate of 61. On aspirates of both left and right knees, Gram-positive cocci were seen. Cultures of blood specimens drawn on admission and of aspirates from the left and right knee both grew Staphylococcus aureus with the identical penicillin-resistant tetracycline sensitive organism. Antibiotic sensitivities were identical for all organisms cultured in the blood and knees. Therapy was started with 1 gram of cloxacillin given intravenously every four hours. On x-ray studies of both knees only soft tissue abnormalities were seen and there were no findings indicative of osteomyelitis.

The day following admission, incision, drainage and debridement with closed tube irrigation of both knee joints were done. Approximately 400 cu cm of purulent material was found in each knee joint, as well as soft tissue inflammation and debris. Postoperatively, in addition to continua-

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tion of intravenous administration of cloxacillin, each knee joint was irrigated with 50 cu cm of normal saline solution containing 100 mg of cloxacillin, administered over 30 minutes every three hours. The patient's temperature returned to normal three days postoperatively and symptoms subsided quickly, with little or no clinical effusion on either knee. The abscessed tooth was removed during the hospital stay, and cultures were negative although the patient had been treated with cloxacillin for four weeks.

Peak serum bactericidal tests on specimens drawn one hour after intravenous antibiotic administration, and 15 minutes before the next dose, showed average killing levels of 1:256, with valleys never below 1:8. After the fourth week, the patient's knees were passively exercised several times a day through a range of motion.

In the sixth week after intravenous administration of cloxacillin was begun, a saline wash-aspiration of both knee joints was done and cultures showed no growth of the organism. The patient was discharged from hospital and a regimen of orally given cloxacillin was begun. Twelve weeks postoperatively the range of motion was 0 to 85 degrees in each knee. The patient was free of pain and able to walk with a cane. There were no joint effusions, localized symptoms or evidence on x-ray studies of osteomyelitis.

Comments

This case shows that hematogenous spread of infection to a prosthetic joint can occur. It is important for physicians and dentists to be aware of this fact when a patient with a prosthetic joint replacement is seen.

There are only a few case reports[5,6] which show hematogenous spread of infection to a prosthetic joint; however, postoperative infection does occur for an indefinite period of time.[2] Hall[5] reported a late infection of a total knee prosthetic implant secondary to a urinary tract infection five years postoperatively. Amstutz[7] pointed out that most postoperative hip replacement infections in one series were associated with simultaneous urologic infection. Although there are very few case reports of hematogenous spread of infection to orthopedic implants, the rate of delayed infections varies from 0.5 to 5 percent. Surely at least some of these are of hematogenous origin.

The incidence of late sepsis in orthopedic implants seems to be similar to that found after valvular replacement in cardiovascular surgical procedures.[8-11] Approximately 40 percent of the infected cardiac prosthetic implants are clinically apparent two or more months after operation. The types of bacteria found in infected orthopedic prosthetic devices are similar to those that cause infection in cardiac prosthetic implants[8-12] and are, coincidentally, the same bacteria that can be cultured from the operating room.[12] In one series,[12] 30 percent of 658 routine cultures taken at the time of total hip replacement were positive. Of 14 patients in whom there were later infections, only in one patient was the same organism present at the time of infection as found during the routine culture taken at the time of operation. The incidence of infection in patients with rheumatoid arthritis is unusually high, whether spontaneous[13] or after orthopedic procedures.[14,15] It is well-known that patients treated with corticosteroids are at risk to infection, while the presence of a rheumatic disease itself may predispose to infection.[16]

Summary

A 61-year-old woman presented with pain and swelling in both knees a year and a half after bilateral knee joint replacements. Aspiration showed the presence of infection, which was linked to a prolonged tooth abscess. This case illustrates a hematogenous spread of infection to prosthetic joints.

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Severe Coombs Negative Hemolytic Anemia in Hepatitis B

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ALTHOUGH 25 PERCENT of patients with viral hepatitis have a slightly shortened erythrocyte survival time, severe hemolytic anemia rarely complicates viral hepatitis in the absence of preexisting red cell defects or chronic liver disease. Only six such cases have been reported. The purpose of this report is to describe the clinical course and management of a patient with hepatitis B who did not have congenital red cell enzyme deficiency or a membrane defect but in whom severe Coomb's negative hemolytic anemia and renal dysfunction developed.

Report of a Case

A 17-year-old white girl was transferred to the University of California, Los Angeles, Center for Health Sciences (UCLA-CHS) because of intense jaundice, severe pruritus and a profound hemolytic anemia. She had been well until five weeks before admission when an urticarial rash developed. Fourteen days later she had been admitted to another hospital because of jaundice, fever, chills, nausea and vomiting. The patient was known to use intravenous narcotics and hallucinogenic drugs, but had been receiving no other medications.

On physical examination, the patient was seen to be jaundiced. The liver was tender and had a span of 15 cm in the right midclavicular line. Laboratory studies showed the following values: serum glutamic oxaloacetic transaminase (SGOT), 8,320 international units (IU) (N = 20-55); alkaline phosphatase, 290 IU (N = 45-105); total bilirubin, 9.6 mg per dl (N < 1.2)—direct fraction 8.0 mg per dl (N < 0.35), and positive hepatitis B surface antigen (HBsAg) by radioimmunoassay. The patient was discharged after six days when nausea and vomiting stopped.

Three days after discharge the patient was readmitted because of increasing jaundice. Liver function studies showed the following values: SGOT, 678 IU; serum glutamic oxalic transaminase (SGPT), 780 IU (N = 10-40); total bilirubin, 21.4 mg per deciliter; direct bilirubin, 11.4 mg per dl; prothrombin time, 100 percent of control. The hematocrit reading was 29 percent; leukocyte count was 4,900 per cu mm. Results of examination of a percutaneous liver biopsy specimen showed a mononuclear cell infiltrate in the portal tracts, lobular disarray, and some peripheral collapse. The next day the hematocrit reading decreased to 17.5 percent, the bilirubin value increased to 49 mg per dl and SGOT decreased to 113 IU. Other study findings included direct and indirect Coombs test, negative; glucose-6-phosphate dehydrogenase (G6PD), level normal, and reticulocyte count, 0.6 percent. Eight units of packed cells were transfused during the next 12 days to prevent severe anemia.

On physical examination after transfer to UCLA-CHS, the patient was found to be depressed and deeply jaundiced. A macular rash was noted on one arm. The abdomen was soft and not tender, the liver span measured 15 cm at the right midclavicular line and the tip of the spleen was palpable. Laboratory studies showed the following values: total bilirubin, 29.0 mg per dl—direct fraction 21.0 mg per dl; SGOT, 185 IU per liter; SGPT, 160 IU per liter; alkaline phosphatase, 280 IU per liter; total protein, 7.0 grams per dl; albumin, 4.2 grams per dl; prothrombin time, 11.5 seconds—control 11.6 seconds; HBsAg positive by radioimmunoassay; hemoglobin, 9.9 mg per dl; hematocrit, 28.4 percent; reticulocyte count, 0.4 percent; a leukocyte count of 5,400, 59 percent segmented cells, 7 percent band cells, 4 percent eosinophils, 16 percent lymphocytes, 9 percent monocytes and 5 percent metamyelocytes; a platelet count of 410,000; results of direct and indirect Coombs' tests, negative by standard clinical laboratory techniques; serum haptoglobin, 0 (N = 20-200); plasma hemoglobin, 14.9 mg per dl (N < 0.9); G6PD spot test, normal; monospot test, negative; serum iron, 137 micrograms (μg) per dl (N = 65-175); total iron binding capacity, 318 μg per dl (N = 250-400); serum

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folate, 19 ng per ml (N=5.6-21); serum vitamin B_{12}, 747 pg per ml (N=330-1,025); BUN 43 mg per dl (N=9-20); creatinine, 2.3 mg per dl (N=0.7-1.3); creatinine clearance, 35 ml per minute.

Dipstick examination of the urine for hemoglobin (Bibilastix®, Ames Co., Eckhart, Indiana) indicated the presence of a large amount. Examination of bone marrow aspirate showed notably increased erythroid elements. Examination of peripheral blood smears showed polychromasia and basophilic stippling of red blood cells, lymphocytes appeared normal. Sucrose hemolysis screen was negative. Red cell half life was 10 to 12 days determined by ^{51}Cr tagging technique.

Although reticulocytosis appeared on the patient's third hospital day, the hematocrit reading decreased from 28 to 16 percent during the first week and then began to increase; transfusion was not carried out. The reticulocyte count increased from 0.7 to 24 percent. Renal tubular dysfunction due to hemoglobinuria was treated with 3,000 ml per m^2 of surface area per day of intravenously given 5 percent solution of dextrose in water containing 50 milliequivalents per liter of sodium bicarbonate ($NaHCO_3$) to alkalinize the urine.

Eighteen days after admission, repeat studies gave the following values: SGOT, 65 IU per liter; total bilirubin, 5.0 mg per dl—direct bilirubin, 4.0 mg per dl; hemoglobin, 8.1 grams per dl; hematocrit reading 23.4 percent; serum hemoglobin, 0, blood urea nitrogen (BUN), 19 mg per dl, and creatinine, 1.6 mg per dl.

The patient was seen one month after discharge. She was asymptomatic and findings on physical examination were normal. Finding from laboratory studies included: SGOT, 32 IU per liter; SGPT, 44 IU per liter; alkaline phosphatase, 122 IU per liter; total bilirubin, 1.0 mg per dl; hematocrit reading, 34.6 percent; haptoglobin, 121 mg per dl; reticulocyte count, 1.6 percent, and creatinine, 1.0 mg per dl.

Discussion

Acute severe hemolytic anemia is a very rare complication of acute viral hepatitis in the absence of chronic liver disease or preexisting hemolytic disorder. Oesman[1] reported the case of a 6-year-old child in whom the hemoglobin value decreased to 6.0 grams per dl with viral hepatitis. In this case the indirect Coombs' test gave positive findings and the marrow appeared hyperplastic. Raffensperger[2] reported three cases of viral hepatitis in which results of direct Coombs' tests were negative for hemolytic anemia. Two of the three patients were children and in one of them there was histologic evidence of chronic liver disease. Wagner[3] reported the case of an 18-year-old patient in whom results of direct Coombs' tests were hemolytic positive for hemolytic anemia and in whom a prolonged aplastic phase occurred which required multiple transfusions. Hansbarger[4] reported two cases, both with negative findings on Coombs' tests, in which the hemoglobin decreased to 5.0 and 5.9 grams respectively. Erythroid hyperplasia was observed on marrow aspiration.

Severe hemolytic anemia is a more frequent complication of viral hepatitis in patients with glucose-6-phosphate dehydrogenase deficiency, beta thalassemia and congenital nonspherocytic anemia.[5-7]

Subclinical hemolysis has been shown to occur in 25 to 50 percent of patients with uncomplicated viral hepatitis.[8] The hematocrit reading is often slightly decreased during the second and third weeks of jaundice.[9] Reticulocytosis follows the onset of the decreased hematocrit by approximately one week. This delay is due to marrow suppression caused by hepatitis. The cause of the hemolysis is unknown. It occurs with both homologous and autologous cells to the same degree, implicating an extracorpuscular factor. This could be due to circulating antibodies or to a direct effect of the virus upon the red cell. This phenomenon usually lasts for one to two months but may persist for up to two years.[7]

Our case is similar to the others in which severe hemolysis was present. The severity of the hemolysis was not related to the degree of hepatitis. Hemolysis persisted for six weeks before the hemoglobin and hematocrit values began to increase. The patient's complete recovery, with normal haptoglobin and reticulocyte count, is evidence against preexisting hemolytic disease. The contributions of marrow suppression to our patient's anemia is difficult to assess because bone marrow aspiration was carried out late in the course of her disease.

Hemolysis of transfused packed red blood cells may have temporarily worsened this patient's condition. Transfusion should be given in such patients only when symptoms develop due to the anemia because the increased hemolysis may result in hemoglobinura and renal failure. The decrease in creatinine clearance in our patient

most likely resulted from the hemoglobinuria. Generous hydration and alkalinization of the urine are then necessary to prevent precipitation of casts and resulting renal damage.

ADDENDUM: Additional follow-up studies could not be made in the case discussed because the patient was killed in an automobile accident one month after her last visit to the clinic.

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Refer to: Bernhardt IB: Mucocutaneous lymph node syndrome with encephalopathy in the continental United States. West J Med 125:230-233, Sep 1976

Mucocutaneous Lymph Node Syndrome with Encephalopathy in the Continental United States

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RECENTLY, three papers have appeared in the pediatric literature calling attention to acute febrile mucocutaneous lymph node syndrome (MLNS),[1-3] an illness that previously had been seen only in Japan and Hawaii. This illness is an acute febrile mucocutaneous condition accompanied by swelling of cervical lymph nodes. Fatalities were reported in 1 to 2 percent of cases.[1] In each instance, the cause of death was proved to be myocardial infarction secondary to coronary thromboarteritis. The findings were almost indistinguishable from those of infantile polyarteritis nodosa.[4] Fetterman and Hashida[5] commented, "Whether or not MLNS is a problem of any degree in the continental United States . . . should become apparent within the next year or so." Reported here is a case of MLNS that occurred in the San Francisco Bay Area in May 1975. The illness was consistent with that described by Kawasaki and colleagues[1] on the basis of their experience, their review of the Japanese literature, findings from a Japanese public health survey that included nearly 4,000 cases and their awareness of more than 6,000 cases reported up to 1973. An additional manifestation in the infant described here was focal encephalopathy.

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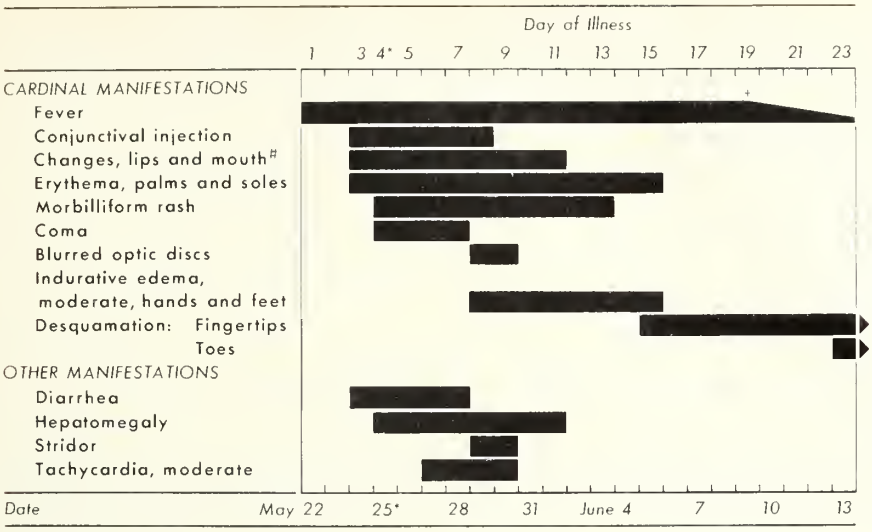
Report of a Case

An 8-month-old white girl was admitted to Kaiser Foundation Hospital, Santa Clara, California, on May 25, 1975 because of high fever, seizures, apnea, rash and diarrhea. On May 19 (four days before admission), ampicillin had been given for an ear infection. When the infant was seen as an outpatient on May 24 (one day before admission), fever, a macular rash on the arms and diaper area, and conjunctival injection were noted. Because measles was suspected, the ampicillin was discontinued. On May 25, before the patient was admitted to hospital, four generalized tonic-clonic seizures and a period of apnea necessitating resuscitation had occurred.

When admitted the patient was comatose and febrile, and a generalized macular morbilliform rash was seen to be present. Noted were conjunctival injection, erythema of the buccal and pharyngeal mucosa, swelling and prominence of the tongue papillae simulating strawberry tongue, and cervical lymphadenopathy. The liver edge was palpable 4 cm below the costal margin. The palms of the hands and soles of the feet were erythematous. The present illness was considered to have started May 22, the first day of fever. The clinical features and the duration of each are shown in Figure 1. Details not evident from the figure are given below.

From the 1st day of illness through the 18th,



*Admitted to hospital.
†Fever began to abate.
#Protuberance of tangue papillae (strawberry tongue), erythema of buccal and pharyngeal mucosa

Figure 1.—Times of appearance and disappearance of manifestations of mucocutaneous lymph node syndrome in an 8-month-old infant.

ABBREVIATIONS USED IN TEXT
IPN=infantile polyarteritis nodosa
MLNS=mucocutaneous lymph node syndrome

the temperature spiked from 36.7 to 39.2°C (98 to 102.5°F). Starting on the 19th day, it underwent a slow spiking descent, reaching normal by the end of the 22nd day.

The infant was comatose to semicomatose on the day of admission, then slowly regained consciousness and was normally alert by the end of the fifth hospital day (days 4 through 8 of the illness). An electroencephalogram on the seventh day of illness showed occasional recurrent spikes over the right parietal area. The cerebrospinal fluid contained 21 mg of protein per dl; 5 mononuclear cells and 105 red blood cells per milliliter. Cultures of the fluid grew no organisms. No abnormalities were seen on brain scan. Administration of diphenylhydantoin was started. The optic discs were noted to be blurred on the eighth and ninth day of illness. Findings on electroencephalogram on the 18th day of illness were normal. No abnormality was seen on a chest roentgenogram or on serial electrocardiograms.

Figure 2.—Desquamation of toes, which started on the 23rd day of illness.

Slight desquamation of the trunk started on the 11th day of illness; desquamation of the fingertips started on the 15th day and of the toes on the 23rd day (Figure 2).

Representative findings in studies of blood and urine are shown in Tables 1 and 2. Briefly, there were the following findings: peripheral leukocytosis with neutrophilia, accelerated erythrocyte sedimentation rate, anemia, leukocytes in the urinary sediment, minimal proteinuria, serum glutamic oxalic transaminase (SGOT) elevation, positive C-reactive protein, negative antistreptolysin-O titer, and increased α_2 globulin. Serologic studies were negative for influenza A, influenza B, adenovirus, mycoplasmal pneumonia, respiratory syncytial virus, measles, rubella and cytomegalic inclusion virus.

Therapy directed toward the symptoms of MLNS included administration of ampicillin, dexamethasone and diphenylhydramine hydrochloride. The infant's condition slowly improved and she was

TABLE 1.—*Representative Findings in the Blood of an 8-Month-Old Patient with Mucocutaneous Lymph Node Syndrome*

	Cell Count per ml								
Day of Illness	*Leukocytes*	*Polymorphonuclears*	*Non-segmented Neutrophils*	*Lymphocytes*	*Monocytes*	*Eosinophils*	*Metamyelocytes*	*Hematocrit Percent*	*Hemoglobin g/dl*
4	13,800	29	51	17	1	..	2	30	10.3
5*	8,800	39	31	22	5	..	3	32.1	10.6
9	24,100	70	15	12	1	1	1	27.2	8.6
12†	17,800	60	5	26	3	2	2	27.7	8.7
13‡	13,700	49	12	34	4	..	1	25	8.0
19§	20,000	53	12	29	6	..	..	27.5	8.5

*Platelet count, 314,000/ml.
†Erythrocyte sedimentation rate, 57 mm/hr.
‡Reticulocyte count, 4.9 percent.
§Erythrocyte sedimentation rate, 63 mm/hr.

TABLE 2.—*Representative Urinary Findings**

				Cells in Sediment/hpf		
Day of Illness	*Specific Gravity*	*pH*	*Protein*	*Leukocytes*	*Erythrocytes*	*Casts*
5 (a.m.)	1.015	5	2+	25-35	..	25-50†
(p.m.)	1.028	5	1+	60-80	..	2- 5‡
6	1.002	5	..	..	..	..
7	1.021	5	..	30-40	..	..
8	1.010	6	..	30-40	..	..
9	1.007	7	..	15-20	..	..
11	1.012	..	..	5- 9	3-5	2- 5§

hpf = high power field

*Suprapubic urine collection showed no bacterial growth.
†Hyaline and fine granular casts.
‡Hyaline and granular casts.
§Hyaline casts.

discharged two and a half weeks after admission. Therapy with diphenylhydantoin has been continued, and there have been no further seizures. The patient now appears well.

Discussion

This patient's illness included the following "principal symptoms" listed by Kawasaki and coworkers:[1] (1) fever lasting three weeks and not responding to therapy with antibiotics, (2) bilateral congestion of ocular conjunctivae, (3) changes of lips and oral cavity (dryness, redness and fissuring of lips; protuberance of tongue papillae resembling strawberry tongue; diffuse reddening of oral and pharyngeal mucosa), (4) changes of peripheral extremities (reddening of palms and soles; indurative edema; membranous desquamation from digit tips), (5) polymorphous exanthema of body trunk without vesicles or crusts and (6) minimal nonpurulent swelling of cervical lymph nodes (no large nodes were noted).

In only 75 percent of the cases reported by Kawasagi and colleagues[1] was there swelling of the cervical nodes; whereas all of the other findings occurred with greater frequency. In 60 percent of the patients, all of the principal manifestations occurred; one or two manifestations were lacking in the remaining cases.

The illness in the case reported here also included the following "other significant symptoms or findings" mentioned in these workers' description of MLNS:[1] (1) diarrhea, (2) proteinuria and increased number of leukocytes in the urinary sediment, (3) changes in blood test values (leukocytosis with shift to the left, slight decrease in erythrocyte and hemoglobin levels, increased erythrocyte sedimentation rate, positive C-reactive protein, increased α_2 globulin, negative antistreptolysin-O (ASLO) titer and slight increase in the SGOT.

Encephalopathy first occurred on the day of hospital admission, the third day of the illness. A lowered level of consciousness persisted for four days. Abnormalities on electroencephalogram were noted, and anticonvulsant therapy was begun and continued. No further seizures have been observed.

There was no evidence of carditis other than moderate tachycardia. No abnormalities were seen on x-ray studies of the chest or electrocardiograms. The infant is presently in good health.

Serial coronary angiography of 20 survivors of MLNS[6] showed abnormalities in 12 (60 percent). In seven (35 percent), coronary aneurysms were present, two of which regressed. Mitral regurgitation developed in one patient. Fetterman and Hashida[5] cited a Japanese language report by Tanaka[7] about 13 patients studied postmortem who had died of MLNS: thrombotic necrotizing coronary arteritis with aneurysmal dilatation was found in all. Morphologic findings described in reports of fatal MLNS are indeed indistinguishable from those of infantile polyarteritis nodosa (IPN).[5] The diagnosis of IPN has been made antemortem

based on angiographic findings in two children.[8,9] Fetterman and Hashida[5] agreed with Tanaka[7] that a clinical resemblance often exists between IPN and MLNS.

In response to careful inquiry, the parents of the infant in the case reported here stated that they knew of no relatives, neighbors or other persons with whom the family has come into contact who had traveled to Japan or Hawaii.

Summary

An infant seen in the San Francisco Bay Area with signs and symptoms suggesting measles was found to have mucocutaneous lymph node syndrome (MLNS) with an additional feature, focal encephalopathy. Therapy with antibiotics, adrenocortical steroids and antihistamine was used. Improvement in the condition of the patient occurred during two and a half weeks in hospital. Anticonvulsant therapy is being continued. Seven months after the onset of the illness no sequelae are evident.

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Pointers in Antianxiety Pharmacotherapy

A cause for concern is if the condition of a patient is temporarily stabilized on a specific dosage of medication, but he then begins to request an increased dosage. This means to me either worsening of life stresses, deterioration of psychological coping mechanisms (perhaps indicative of a more serious mental disorder), or the developing of abuse and addiction. Sometimes the patient will complain that no tranquilizer he has tried is satisfactory, in any dosage, but may keep demanding a different drug and higher doses. This is also indicative of a serious problem. Keep careful records of all prescriptions written, with notations indicating when the patient should be running out of pills . . . be suspicious if a patient tells you he has run out of medication sooner than your records indicate he should, or if he tells you that he has lost his prescription or lost his pills—particularly if this happens more than once. If it does happen more than once, I am certain he is taking more than what has been prescribed. The patient should be confronted with this problem and be advised to seek professional mental health intervention. Another problem which arises not infrequently is a patient getting tranquilizer prescriptions from more than one physician. Sometimes this is because the patient shops around and keeps it a secret. But other times this is the result of insufficient communication between the family physician and the psychiatrist or mental health agency to which the patient is referred. The patient may openly continue to see the referring physician who continues to prescribe tranquilizers or sleeping pills while the psychiatrist continues to do the same, neither taking the effort to check what the other is doing with the patient. This problem arises in two ways: The referring physician does not call or write the psychiatrist explaining the reason for referral, but instead just sends the patient to present the problem himself; or the psychiatrist does not recontact the referring physician to work out a joint treatment plan.

—RICHARD M. KETAI, MD, *Ann Arbor*

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Medicine and the Quality of Life

QUALITY OF LIFE increasingly is being identified as a goal of medicine and health care. In the July issue, the editors began a forum for discussing the actual and ideal relationships between medicine and the quality of life by printing seven articles expressing differing views. The following comments were generated by those articles.

Readers are invited to take part in a continuation of this forum by submitting their comments, written as succinctly as possible. As many of these as space permits will be published in future issues. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement to summarize the dialogue that has taken place.

Involvement in National Problems

WILLIAM CAMPBELL FELCH, MD, Rye, NY
Past President, American Society of Internal Medicine

IT IS MY VIEW that the quality of life must be examined both from an individual and a collective viewpoint.

For the individual person, life is of high quality when it contains something to care deeply about, some internally cherished goal. The object can be a thing, a person or a cause. It can be trivial or noble. It need not be lifelong: this season's enthusiasm can be supplanted by next year's passion. Nor need it be attainable: unrequited love has remarkable staying power; indeed, achievement of a long-held dream can end in emptiness. An individual person's passion does not even have to be worthwhile in a social sense: the revenge motive can make its bearer feel intensely alive.

It is much more than just having a purpose, a rational goal. It must have an emotional content, be so deeply cherished that the person can hang on to it when the work-a-day world goes badly. It is an intensely human quality, one which undoubtedly has psychological determinants. Its opposite number is apathy, boredom, depression.

Turning from the individual person to the group, I am inclined to believe that the collective quality of life is not merely the algebraic sum of individual units, the aggregate effect of individual aspiration and apathy. The whole is different from the sum of its parts.

I suspect that there may be a collective subconscious, as some psychiatrists think, which to some degree holds sway over individual attitudes. Or perhaps there is a social contagion through which attitudes spread and infect the group as a whole. Negative examples abound: the pervasive apathy of most geriatric nursing homes, the depressive hostility of the inner-city neighborhood, the post-Watergate cynicism and voter apathy. But there are positive examples as well. Some nursing homes are cheerful and optimistic. Some neighborhoods work together to solve problems. Great social causes sometimes capture the national fancy (the words "we shall overcome" bring to mind one example).

In this bicentennial year, it may be worthwhile to recall the energy of our pioneers, the audacity of our founding fathers, the indomitable drive of our immigrants, the 200-year national motif of striving for excellence. Lest this sound like sheer jingoism, one need only contrast the depressed atmosphere behind the iron curtain or the bland acceptance often characterizing people in the People's Republic of China.

What can the medical profession do to improve the quality of life? At the individual level, I am skeptical about a physician's chances of having much influence on an individual patient's experience of life. Only once in a blue moon do we see a patient really change his lifestyle at our behest. Certainly the physician can do nothing to *create* the passion in his patient; it is usually there or it is not. I suppose that to the degree to which we can influence a patient's health status favorably, we can create a more suitable environment for the spark to thrive in. But there is evidence that physical disability, even constant pain, can be the stress that creates or enhances the spark of life. How often we see a handicapped person filled with the zest to accomplish some goal. It can even be argued that our laudable urge to soothe, by use of tranquilizers or by ironing out peaks and valleys with lithium, may achieve the result of relieving discomfort, but at the cost of inhibiting the creative urge toward accomplishment.

It is at the collective level that I see an opportunity for the medical profession to improve the quality of life, through a process of stimulating change in public attitudes about issues. For too long we have been passive observers of the social and political scene. Our profession's posture has been one of detachment, perhaps caused by our need to be scientific and rational, maybe even our desire to have it appear that we think about things rather than care about them. Even in medical matters, we are wont to offer pros and cons instead of taking a stand. In political matters, we only get involved in those matters affecting us, and thereby end up in a reacting and self-serving posture.

My proposal is that we, the collective medical profession, should get involved in *all* the problems of the day, not only the giant issues of poverty, hunger and social injustice, but also such matters as busing, gun control and drunken driving. We should take stands on *all* issues and offer them to the public with conviction. It is my expectation that our positions will probably be sensible and will be listened to, partly because we understand the analytical, decision-making process, and partly because our everyday work makes us expert in the human condition.

To accomplish this will not be easy. Difficult positions cannot be reached through meetings of a house of delegates or by a popular vote. I would suggest formation of a national academy, admittedly an elite body, made up of physicians of intellectual breadth and practical wisdom, mostly coming from the broad practice of medicine rather than from academia. Its members, after staff research, would take a stand on issues, obviously not representing the profession's consensus, and obviously subject to individual and factional disagreement. But at least clear stands would be taken. And, just possibly, they could change public attitudes in a positive direction and thereby improve the quality of life.

Refer to: Felch WC: Involvement in national problems, *In* Medicine and the quality of life—A forum. West J Med 125: 234, Sep 1976

The Team Approach

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THE DUTY of the medical profession is two-fold: the prevention of disease and injury and the restoration of health or tolerable physical well-being to those persons who have lost it through injury or disease. Obviously, the attainment of these objectives contributes, and has contributed, enormously to the quality of life both for individual persons and for the community as a whole. However, as Professor Dubos pointed out in the July issue of this journal, the role of physicians cannot include all aspects of the adjustment of human beings to the shocks and vicissitudes of this world. Even the kindliest and most sympathetic of family physicians cannot assume the role of minister, priest, family counselor and social worker for every patient he sees. His education does not qualify him to do so and time so spent would be a costly distraction from those tasks for which he is fitted and needed.

On the other hand, physicians and surgeons should always see a patient as an anxious, concerned person who needs the sympathy and understanding of his doctor as much as he needs his scientific and technical skill. The art of medicine requires a physician to see a patient not as a disease but as a disturbed human being who can be restored to a useful and enjoyable life only by taking into consideration emotional, economic, family and social factors, as well as physical ailments. Often, a good physician can identify problems that, once recognized, can be resolved by others with the time and competence to do so.

In our progressively more complicated society, we in the medical profession can contribute more effectively to the quality of life by developing the team approach with regular participation in the care of patients on the part of allied professionals, especially nurses, social workers and members of the clergy.

Refer to: Dunphy JE: The team approach, *In* Medicine and the quality of life—A forum. West J Med 125:235, Sep 1976

Full-time Attention to Medical Problems

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OVERALL, I could not see that any of the seven statements in the July issue tells us how to improve the quality of life. To understand one human soul is like bailing water out of the ocean with a teacup. As Dr. Moser pointed out "What do you do with a patient who suffers the hellfire of recurring pancreatitis, yet continues to drink alcohol; a patient with chronic obstructive airways disease with recurring bouts of bronchitis, who continues to smoke cigarettes; a businessman with two previous myocardial infarctions, who continues to eat to excess, refuses to exercise and maintains a breakneck pace in his business?" And further how do you get people to wear seatbelts or to drive with care and courtesy?

It seems to me that problems like this transcend the practice of medicine. A career medical officer once told me that the Army represents an ideal health maintenance organization. The soldiers' diet, clothing, shelter and medical care are well controlled. What patients do on their own time is something else again. But these same persons succumb to the same illnesses at about the same time and to the same degree as their civilian counterparts. Excessive drinking, smoking and general carousing can be no better controlled than with their civilian counterparts.

In his article, Dr. Cooper tells us that we can bring to the attention of the public those societal pathogens that may be avoided or eliminated. With this I agree. But then he says that up to 80 percent of all cancer results from exposure to carcinogenic agents in the environment. How does one arrive at such a figure?

Dr. Dubos tells us that physicians cannot judge for society what its future should be; they can only warn that environmental conditions are eventually reflected in the state of health and therefore in the quality of life.

Dr. Fuchs suggests that physicians should consider the possibility of contributing more by doing less. I suppose this is true in the case of the use of drugs that have too low a benefit-to-risk ratio but certainly we do need to do more and not less.

Dr. Elam rightfully points out that practice habits of physicians themselves are destructive because of overwork and yet one has the feeling that in his view psychosocially deprived persons must look to physicians for salvation. What is the role of all social planners, bureaucrats and politicians in all of this? Are they not supposed to be correcting these problems?

Finally, Mr. Sobel seems to feel we should go back to the Stone Age in medicine. This is absurd. There are still a seemingly infinite number of unsolved medical problems; physicians could and should devote their full time to conquering disease. The medical profession certainly cannot cure social woes such as war, pestilence and famine—and all that accompanies them. I think it is correct to state that not one single viral disease, once established, has a "cure" that has a reasonable benefit-to-risk ratio. And of course this observation is just the tip of the iceberg.

Refer to: Rees RB: Full-time attention to medical problems, *In* Medicine and the quality of life—A forum. West J Med 125:235, Sep 1976

LETTERS *to the Editor*

Piriform Syndrome

To the Editor: I read with great interest the article "Piriform Syndrome" in the June issue (West J Med 124:435-439, Jun 1976).

I would like to call to the reader's attention an excellent article by William Hunter, MD, and Adrienne L. Zihlman, PhD, in which they describe diagnosis and treatment in 36 patients with this syndrome.[1]

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San Francisco

REFERENCE

1. Hunter W, Zihlman A: Abdominal pain from strain of intrapelvic muscles. Clin Orthop 71:279-280, Jul-Aug 1970

Preventive Medicine—A Myth?

To the Editor: Like the mercenaries of the federal government, the academicians also chant the litany of practicing preventive medicine. What beautiful pictures they draw. "If physicians devoted as much time, energy and skill to minimize the need for medical care as they now devote to its delivery . . . " goes the chant. Do you know what would happen if we did that? Nothing. Not a blessed thing.

The government has tried, and with one of the most publicized causes of morbidity and mortality in the country—the effects of cigarette smoking. Every package of cigarettes carries the well-known warning. And the result? Smoking continues to increase steadily. The government's effort was a failure.

Every clinician who has worked with his patients to try to get them to lose weight, slow down, give up smoking, start a moderate exercise program or decrease drinking, knows the incredible frustrations and the enormously low return for the effort expended.

In our community, physicians organized a "Home Health Care" lecture series. Put on gratis one evening a week for 13 weeks and publicized in each of the two local papers, we covered one subject a week, including such subjects as pediatric emergencies, adult emergencies, nutrition, skin care, eye care and the like. And the result —no one came. No one really gave a damn.

We have the obligation to continue trying and we will. But the government and the professors should give up this time worn litany. The clinicians know it won't work and the public isn't interested. Until they can come up with a method that works, they should spare us this useless advice.

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Trauma Rounds

Chief Discussant
FRANK LEWIS, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Lewis F: Cold injury in a trauma patient (Trauma Rounds). West J Med 125:237-240, Sep 1976

Cold Injury in a Trauma Patient

JANETH H. ADELSON:* The patient is a 50-year-old black man who was unresponsive when brought to Mission Emergency after falling 25 feet out of a window and lying overnight in the cold. At the time of admission, a medical history was unavailable; subsequently it was found that the patient had a history of alcoholic hepatitis and peptic ulcer disease.

On physical examination the patient remained unresponsive. Blood pressure was palpable at 70 mm of mercury, pulse rate was 110 beats per minute and temperature was 82.4°F (28°C). Respirations were spontaneous but shallow. The fundi were normal. The heart and lungs were not remarkable. The abdomen was slightly distended and epigastric tenderness was present. There was no rebound tenderness. Bowel sounds were absent. On examination of extremities, fractures of the right humerus and right ankle were noted. The pulse was palpable in the neck; the pulses were present but barely palpable in the extremities. The patient moved all extremities and no focal findings were shown on neurologic examination. Laboratory data included a hematocrit reading of 34 percent, which dropped to 24 percent within 12 hours with hydration. Analysis of urine showed no abnormalities. The following were arterial blood gases corrected for temperature as oxygen was being given by nasal prongs: oxygen pressure (Po_2), 160; carbon dioxide pressure, 63, and pH, 7.37. Blood urea nitrogen (BUN) and electrolytes were normal. Serum amylase level was 850. No abnormalities were seen on an x-ray film of the chest. Fractures of the right distal tibia and fibula and right humerus were seen on x-ray studies of the extremities, as well as a comminuted fracture of the right acetabulum.

The patient was taken to the operating room and put on a warming blanket; his temperature was brought to 96.8°F (36°C). On an exploratory laparotomy, carried out because of the fall in the hematocrit value, a retroperitoneal hematoma was noted but no intraabdominal injury. The liver was found to be cirrhotic to a pronounced degree. Following laparotomy the right arm was stabilized by pinning and a fasciotomy was carried out because of swelling of the right forearm. Closed reduction of the right angle fracture was accomplished and a pin was placed in the femur for traction.

The patient awoke postoperatively and was neurologically intact. The endotracheal tube was removed. Following surgical operation, diffuse oozing of blood from cutdowns, needle tracts and incisions was noted and a clinical diagnosis of disseminated intravascular coagulation (DIC) was made. Results of clotting studies included a prothrombin time of 18 seconds, partial thromboplastin time of 75 seconds and a platelet count of 80,000 per cu mm. Fresh frozen plasma, platelet packs and, subsequently, six units of warm fresh

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blood were administered. Heparin (10,000 units) was given by intravenous bolus, followed by 2,000 units every two hours. The arterial Po_2 gradually dropped to 50 despite supplemental oxygen, and reintubation was carried out 12 hours postinjury.

On an x-ray of the chest, bilateral perihilar infiltrates were seen by 24 hours; findings on clotting studies remained highly abnormal for 24 hours and then returned to normal over the next three days. Within 12 hours of surgical operation, the urine became dark and showed a positive reaction for myoglobin. The patient was given 25 grams of mannitol intravenously, followed by an isotonic mannitol drip for the next several hours; there was clearing of the urine. During the second and third postoperative days the patient's general condition improved gradually.

Lung infiltrates were noted to increase on the fourth hospital day and the patient's clinical state deteriorated. Peripheral perfusion and urine output decreased; a Swan-Ganz catheter was placed and pulmonary wedge pressure was raised to 15 to 18 mm of mercury with infusion of Ringer's lactate, without significant improvement. Administration of dopamine was begun at a rate of 5 mg per kg of body weight per minute. Gentamycin and ampicillin were given for possible sepsis. Blood cultures were negative and findings on sputum and wound cultures taken at this time were unremarkable. The bilirubin level rose to 12 mg per 100 ml and the patient was clinically jaundiced. Urine output ceased completely on the fifth day postinjury in spite of vigorous fluid therapy which raised the wedge pressure to 20 to 25 mm of mercury. At this time generalized edema resulted from fluid retention and third space fluid shifts.

Because of the large requirement of fluid to maintain minimal circulatory function and because of the development of severe edema, it was felt that abdominal sepsis was present. The patient was returned to the operating room and the compound fracture sites were inspected and found clean. The laparotomy incision was reopened and general abdominal exploration carried out; no infection was found.

Pulmonary infiltrates became worse from the fifth day onward. Severe progressive hypoxemia developed and positive end expiratory pressure was begun; despite this, an inspired oxygen concentration of 80 percent was required to maintain the Po_2 between 50 and 60. Cardiac output was 11 liters per minute. Extracorporeal membrane bypass was considered, but this was contraindicated by the liver disease and a recent history of bleeding duodenal ulcer. Increased positive end expiratory pressure of 25 to 30 cm of H_2O was begun and a Po_2 of 70 was maintained on 40 percent inspired oxygen. No clotting abnormalities were apparent except for a prolonged prothrombin time. Pulmonary function continued to deteriorate and bilirubin levels rose as further liver failure developed on the sixth and seventh days in hospital. The acute renal failure noted on the fourth day after admission persisted. On the seventh day after admission a Seribner shunt was placed in his arm. Renal dialysis, which was poorly tolerated due to hypotension, was carried out. The patient's condition continued to deteriorate and he died shortly after completion of dialysis. A total of 31 units of blood had been administered in the hospital and the patient's weight had increased by 20 kilograms before death.

Frank Lewis, MD:* The frustrating problem with this patient was that he initially appeared to respond to treatment and then a downhill course began from the fourth postoperative day onward without clearly identifiable cause. Although a moderate amount of soft tissue trauma was present, it was not sufficient to cause this type of clinical course and it is hard to ascribe his death to trauma alone. I think what we are really looking at are complications of hypothermia. The patient's temperature was 82.4°F when first measured some 30 minutes after he was brought to the hospital. We do not know how long he lay on the ground, but we see a number of similar cases of patients admitted following exposure and hypothermia, and the mortality rate is 60 to 80 percent in this group. Patients with hypothermia are arbitrarily defined as those having a core temperature under 90°F on admission. The mechanisms which produce death after accidental hypothermia are complex and have never been well explained. These patients behave differently from those subjected to controlled hypothermia for short periods during cardiac surgical procedures, perhaps due to the difference in the duration of the hypothermia insult. Myocardial dysfunction appears early and death in the first 24 hours is often secondary to cardiac arrhythmia. Multiple organ failure is typical in patients after prolonged accidental hypothermia and is the usual cause of death. Hepatic failure, renal failure,

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pulmonary failure and pancreatitis commonly develop and all of these seem to relate to the tremendous increase in capillary permeability which is a nearly universal clinical manifestation. In the patient discussed today, there were at least 10 to 20 extra liters of third space extravascular fluid. In patients who recover, severe edema lasts for three to five days before diuresis occurs. Our assumption is that endothelial vascular damage with increased permeability is required during the first few days, allowing restoration of normal tissue fluid dynamics. When systemic edema lasts for more prolonged periods before diuresis, the prognosis seems to be poor.

Initial treatment of such patients with hypothermia is rewarming by active or passive methods. The optimal rate of rewarming has been controversial; it has been thought that death from cardiac arrhythmia might result from too rapid rewarming. Theoretically, if active peripheral rewarming is used aggressively, metabolic demand increases disproportionately in skin, subcutaneous tissue and skeletal muscle at the expense of the critical core organs. A survey of the literature suggests that the optimal rate of rewarming is 1 to 2°F per hour. This is not so rapid as to produce metabolic disequilibrium but returns the patient to normal temperature in 4 to 12 hours.

After this step, management of these patients revolves around maintenance of optimal fluid balance and cardiac function. In all patients with severe hypothermia, Swan-Ganz pulmonary artery catheters should be placed; this is the most accurate way to monitor intravascular volume status.

Maintenance of adequate intravascular volume is a two-edged sword in a patient such as this in whom there is an apparent increase in capillary permeability. Excessive fluid administration may exacerbate pulmonary edema and hypoxemia while inadequate replacement may precipitate renal failure. As with hypovolemia of any cause we feel the most reliable clinical indices of adequate cardiac output are good skin perfusion and urine output of 0.5 to 1 ml per kg of body weight per hour. If these can be maintained with normal or low central venous pressure (CVP) and pulmonary artery wedge (PAW) pressures, there is no need to maintain higher cardiac filling pressures. If skin perfusion and urine output are low, we administer crystalloid solution (Ringer's lactate or saline) more aggressively until the desired response is obtained, or until the PAW is 15 to 18 mm of mercury. If cardiac output is still inadequate at that point, we begin administration of cardiac inotropic agents—dopamine or isuprel.

F. WILLIAM BLAISDELL, MD:* *One interesting question, Dr. Lewis, is whether hypothermia caused the disseminated intravascular coagulation which led to the capillary leak, or whether the diffuse vascular damage led to the* DIC.

DR. LEWIS: In this instance, DIC was the first manifestation and the diffuse permeability changes seemed to follow. We do not know which is cause and which is effect, however. Tissue damage may result from the extreme cold and low flow state and this may have activated disseminated intravascular coagulation. It is equally possible that hypothermia causes DIC directly and the vascular endothelial damage is secondary. No one has studied this and investigation is called for.

GEORGE SHELDON, MD:† *Dr. Lewis, how common is this type of injury?*

DR. LEWIS: We see approximately one hypothermic patient a month in the intensive care unit, and in most of these patients there is some evidence of DIC in measures of coagulation. Usually the changes in platelet number and platelet function are the earliest manifestations. I am not aware of any reports in the literature relating DIC to the injury of hypothermia. Our observations suggest that there may be an association.

DR. BLAISDELL: *It is interesting that* DIC *in heat stroke is well-documented, and here is the opposite extreme in which* DIC *also seems to play a major role.*

Dr. Lewis, was there not something that could have been done to improve perfusion when the kidneys began to fail? The diagnosis was prerenal failure initially, since there was an extremely low level of sodium in the urine. Should furosamide or an osmotic diuretic have been administered?

DR. LEWIS: It is impossible to answer that question because there is no reported experience treating the renal failure associated with hypothermia. One may suspect there was renal swelling with increased pressure within the renal parenchyma which compromised perfusion and precipitated renal failure. In most circumstances, volume loading of a patient will prevent the renal failure associated with trauma or major surgical procedures. Since it was not successful here, this may be a

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different problem in that there is a diffuse capillary leak in the kidney, as there is elsewhere, in these patients. At a certain point, the edema generated by the capillary leak may produce enough parenchymal swelling to impair perfusion. It is generally accepted now that there is no value in treating oliguric patients with diuretics such as furosamide in an attempt to convert oliguric renal failure to high output renal failure. I would similarly see no justification for their use here except in an attempt to improve pulmonary function.

DR. SHELDON: *Do you think this urinary problem was related to myoglobinuria?*

DR. LEWIS: In this patient there was not a high concentration of sodium in the urine; therefore, we have to accept the fact that the problem was prerenal, not acute tubular necrosis due to myoglobin. In patients with tubular necrosis there usually is a sodium concentration in the urine in excess of 20 mEq per liter of urine. In this patient there were sodium concentrations in the urine of 3 to 5 mEq per liter.

STEVEN PARKS, MD:* *Neurosurgeons frequently use hypothermia for prolonged periods. Why did this patient have such a severe reaction from cold? I wonder if he could have cold agglutinins which precipitated the vascular lesion or* DIC.

DR. LEWIS: The hypothermia induced in neurosurgical or cardiac surgery patients does not approach the level in today's case. Neurosurgical patients are rarely carried below 90°F, whereas this patient was admitted with a temeprature of 82°F. Sixty-five degrees is the coldest temperature from which anyone has recovered. There is no difference in the mortality when temperatures of 70 to 75°F or 80 to 85° F are present. One of the reasons that alcoholics are usually involved in this problem is because alcohol produces peripheral dilation and promotes heat loss. Other patients can shiver, vasconstriction occurs and there is some protection. The accidental hypothermia syndrome is seen in almost no other group but alcoholics.

The question of cold agglutinins is an interesting one. They were not measured here.

DR. BLAISDELL: Dr. Lewis, I wish to thank you for an excellent review of a complex and poorly understood problem. If I may summarize your discussion, the conclusions are as follows. Hypothermia or cold injury occurs as a result of exposure in alcoholics and carries the potential for high mortality and morbidity when body temperature falls below 85°F. Early death usually results from cardiac arrhythmia and later death from multiple organ failure. Rewarming is carried out optimally by either active or passive techniques as necessary to keep the rate at 1 to 2°F per hour.

In patients with severe injury, disseminated intravascular coagulation (DIC) and a diffuse increase in capillary permeability often occur. Vascular volume must be maintained and the patients carefully monitored to avoid too great an infusion of fluids and pulmonary failure on one hand, and hypovolemia and solid organ failure on the other.

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Refer to: Sanazaro PJ: Medical audit, continuing medical education and quality assurance. West J Med 125:241-252, Sep 1976

Special Article

Medical Audit, Continuing Medical Education and Quality Assurance

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Medical audit and continuing medical education (CME) are now the mainstays of quality assurance in hospitals. Audits should address problems that have serious consequences for patients if proper treatment is not given. The single most important step is the selection of essential or scientific criteria that relate process to outcomes. CME does less than commonly believed to improve care. Today, quality assurance increasingly means a near-guarantee to every patient of appropriate treatment and fewest possible complications. Maintenance of the public trust rests on a firm commitment of the medical staff and board to this principle, implemented through an organized program of quality assurance. Under these conditions, medical audit and CME can effectively improve care by improving physician performance.

TWENTY YEARS AGO, Lembcke systematically described medical auditing by scientific methods.[1] Today these methods are widely used and abused in assessing the technical quality of care. Medical auditing is done in most hospitals because the Joint Commission on Accreditation of Hospitals (JCAH) and the Professional Standards Review Organization program (PSRO) both require it.[2-4] Along with this, continuing medical education (CME) is universally endorsed as the principal vehicle for maintaining medical competence.[5] Considering the enormous amount of time and effort devoted to these activities nationally and the public's expectations of benefit from the results, we should critically examine the effectiveness of audit and CME in improving patient care by improving physician performance. At stake is the medical profession's continuing autonomy in assuring the quality of care.[6]

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Medical Audit

The purpose of auditing is to assure that patients with specified conditions are receiving the full benefit of medical care with the least possible number of complications. The techniques for doing this are imperfect and are not standardized, despite the seemingly clear-cut methods described in official publications.[2,7,8] Being retrospective and dependent entirely on information contained in the record, auditing can only assess limited aspects of the technical quality of care. Of central importance are the procedures for selecting a topic and adopting objective criteria. The proper approach to these two steps is a necessary condition for effective auditing directed to improving physician performance.

ABBREVIATIONS USED IN TEXT

CME = continuing medical education
JCAH = Joint Commission on Accreditation of Hospitals
PAS = Professional Activities Study
PEP = Professional Evaluation Procedure
PSRO = Professional Standards Review Organization
QAM = Quality Assurance Monitor
RCT = randomized controlled trials

Selection of Topic

Medical audits should only examine *important* areas of care as originally suggested by Williamson.[9,10] The disease or condition chosen should be curable, controllable or preventable. That is, an effective treatment or preventive measure exists for that condition which produces predictable clinical results or outcomes. Also it should be an established fact that patients suffer serious consequences—complications of the disease or of the treatment, or both—if that treatment is not given properly. Priorities for possible audit subjects are decided on the basis of these considerations, as well as knowledge or suspicion of a particular problem. Selecting audit topics in this way assures the validity of the results and increases the likelihood of medical staff commitment to taking any needed corrective action.

Secondary requirements in selecting topics are *precision of diagnosis* and *frequency*. Audits can be best applied to precisely defined primary diagnoses—for example, bacterial pneumonia of specified bacterial origin rather than all types and causes of pneumonitis, or, diabetes mellitus with ketoacidosis. The presence and severity of each diagnosis, condition or complication should be capable of objective confirmation, preferably by quantitative data. For example, one audit committee specified a blood glucose value of 200 mg per 100 ml or more plus a serum acetone value greater than 1:4 or blood pH less than 7.32, or both, as substantiating the diagnosis of diabetes mellitus plus ketoacidosis. Subdividing a diagnosis or condition into objectively specifiable manifestations, stages of severity or complications facilitates auditing and eliminates some of the drawbacks in using criteria.[11]

The trade-off between importance and frequency in selecting a topic is straightforward. The more serious the consequences for any patient receiving inadequate or inappropriate treatment, the fewer the cases needed for a worthwhile audit.

Adoption of Criteria

More than anything else, it is the type of criteria and the method of adopting them that determine the effectiveness of an audit in documenting whether medical care in the hospital meets high contemporary standards. Some physicians still question the necessity of objective, written criteria, claiming they can readily and accurately judge the quality of care by reading their colleagues' charts. To a certain extent this is true. But the implicit criteria of quality which each physician carries with him may not be widely shared. Even physicians within the same specialty can differ surprisingly in their judgments regarding the quality of care as reflected in a particular record. Richardson found that as many as 16 to 28 physicians would have to read and judge each record to be 95 percent certain that care for that patient was or was not adequate.[12] It is clearly impossible for physicians to devote this much effort to such a task, and the alternative now in general use is to specify explicit, written criteria. These criteria enable nonphysician personnel to screen large numbers of records to identify potential instances of substandard care. Only those records so identified are then subjected to peer review.

Whether the audit can be relied upon for evaluating physician performance and identifying important problems in patient care depends entirely on the method of choosing criteria. As shown in Table 1, there are only three basic types of criteria: *statistical, normative* and *scientific*. An understanding of their source and significance for purposes of quality assurance is necessary for making effective use of the audit.

TABLE 1.—*The Basic Types and Sources of Criteria for Medical Audits*

Type of Criteria	*Source*
Statistical (empirical)	Regional or national statistics on length of stay, current practices, complications, mortality
Normative (consensus)	
Optimal care (general consensus)	Consensus of physicians on procedures that constitute good medical care for a particular condition
Essential (critical)	Consensus of experts in a particular disease or condition on efficacious treatment and achievable clinical results for that condition
Scientific (validated)	Clinical research that objectively establishes the efficacy of treatment and its clinical results in specific conditions

Statistical criteria (also called empirical criteria) *are derived from statistics on actual practice.* They define what physicians presently do in the care of their patients. These statistics may come from the individual hospital's records or, more commonly, from hospital data abstracting systems, like Professional Activities Study (PAS) or California Health Data Corporation. The most widely used are the PAS regional statistics on length of stay.[13] According to these, the average length of stay is longest in the East (8.3 days) and shortest in the West (6.2 days). Because of this, the PSRO program permits regional variations in setting criteria for length of stay. These differences have never been adequately explained, but they apparently do not relate to variations in quality of care.

When national statistics on hospital care are based on a large and reasonably representative sample of hospitals, they may be taken as representing average physician performance. Examples of these are the 25th to 75th percentiles for a number of procedures as reported by the Quality Assurance Monitor (QAM) of PAS.[14] According to the QAM reports, culture and sensitivity determinations are done in 14 to 39 percent of adult patients with pneumonia; in adult patients with acute pyelonephritis, the figures are 43 to 66 percent. If audit committees accept these statistics as reference points for setting their own criteria, they are equating the existing *average level of practice* with the *desired level of quality.* Adopting such statistics amounts to endorsing the status quo. It is doubtful that any specialty or professional organization would endorse the national averages as characterizing quality of care. In short, statistical criteria may be useful in initially assigning lengths of stay, but they are not suitable for auditing the technical quality of care.

TABLE 2.—*Optimal Care Criteria for Acute Urinary Tract Infection*[16]

Criterion	*Percent Observed*
History:	
Urination frequency	14
Obstructive symptoms	26
Pain	71
Hematuria	29
Pattern of incontinence	12
Chronology	86
Previous urologic disease	56
Physical Examination:	
Digital rectal and/or pelvic	37
Bladder examination	27
Kidney area examination	59
Laboratory:	
Urinalysis with stain sediment or culture	74
Urine culture	70
Sensitivity	49
Complete blood count	87
Renal function test	42
Intravenous pyelogram unless prostatitis	36
Antibacterial therapy within one hour	68
Average Percent Observed	56

Normative criteria (or consensual criteria) *represent the judgment of physicians regarding what ought to be done* in the care of patients with certain diagnoses. There are two varieties of these. *Optimal care criteria* (or general consensus) incorporate the consensus of judgments by physicians regarding the elements of good or optimal medical care for a given condition. *Essential criteria* are developed by experts in the diagnosis and management of the particular diseases or conditions being considered.

The most widely used normative criteria are optimal care criteria, first developed by Payne in Michigan.[15] These are the ones referred to as "cookbook medicine" or "laundry lists"; they cannot be used to assess the technical quality of care. For example, in Table 2 are shown optimal care criteria for acute urinary tract infection as proposed and agreed upon by a committee of physicians.[16] The items represent local consensus on the best care for that condition. The figure to the right of each item in the table is the percent of charts in which that criterion was actually observed. Not a single criterion was met in 100 percent of charts, and the average for the study was 56 percent. Similar results were found when optimal care criteria were applied to 20 other diagnoses; an overall average of 71 percent was observed. Similar discrepancies between what physicians propose as elements of good care and what those same physicians actually do in the care of patients were reported by the American Society of Internal Medicine and by the American Academy of Pediatrics.[17,18]

This seems to pose a serious dilemma: If committees of physicians develop criteria for good care, and if these same physicians actually abide by fewer than 100 percent of their own criteria, then, by definition, does that not mean that their care is substandard? The fact is, the dilemma is a purely semantic one: there is no way of knowing whether the care of *individual patients* is optimal when the audit uses so-called optimal care criteria.

There are two specific reasons for this. The first is that this type of criteria evolved from a study

whose primary concern was the effective use of hospitals.[1,9,19] They were actually utilization criteria, intended to make certain that third parties would not deny payment for any procedures listed for particular diagnoses. Consequently, the original sets of criteria from Michigan contain all procedures that *might be necessary* in diagnosing or treating all patients with a particular diagnosis. The criteria are useful to fiscal intermediaries in deciding whether or not to pay for a procedure because their only consideration is that the procedure be consistent with the diagnosis. But when such lists as shown in Table 2 are used in a medical audit, there is no way of knowing *which* of the listed procedures was *essential for the appropriate management of a particular patient.* That is why Brook found that only 1 to 2 percent of the records in his study contained all the optimal care criteria listed by faculty members as assuring quality care.[20]

The second reason that these criteria are not suitable for evaluating the care given individual patients is the tendency to use the audit as an educational vehicle to promote better workups and writeups. The criteria often include a number of symptoms and signs whose presence or absence "should be recorded." But because no two physicians arrive at a diagnosis in the same way, audits which include such educationally-oriented items only show what everyone already knows: There is less in the record than should be there ideally.

The fundamental shortcoming of optimal care criteria is their lack of relationship to outcomes.[20] No matter how many or how few of the criteria are observed, there is little demonstrable relationship to the clinical results. In fact, the correlations can be negative, meaning that the larger the number of criteria met in the care of patients, the less favorable is the result.[16] When adherence to a set of criteria cannot be shown to produce good results in individual patients, audits based on such criteria do little to promote quality of patient care.

In contrast, *essential criteria* are indispensable to an effective audit. *Essential criteria* (also called critical criteria) *apply to almost every patient with a specified condition because they stipulate elements of care known to produce the desired clinical results in patients with that condition.* For this reason, essential criteria enable the medical staff to determine whether care of individual patients, and the results of that care, conform to contemporary high standards. The distinction between essential criteria and optimal care criteria was clarified by the efforts of Experimental Medical Care Review Organizations, originally those in Albemarle County (Virginia), Hawaii and Utah and, more recently, in Southern California.[11,21-23] The concept is promoted by the JCAH through the "critical management criteria" of its own audit format.[2] Private Initiative in PSRO, a national project supported entirely by the W. K. Kellogg Foundation, is currently testing the applicability of essential criteria to concurrent monitoring of care.[6]

When used in a retrospective audit, essential criteria specify the objective data or information needed to:

- substantiate the diagnosis and the presence or absence of complications or other conditions which influence treatment and prognosis;
- document that each patient received treatment of established efficacy, given properly or to the proper end point;
- document that each patient did not receive contraindicated treatment;
- document that the expected clinical results were achieved in each patient.

Essential criteria apply to "almost every patient" because they permit precise specification of a condition and incorporate only those elements of treatment known to be effective in producing the desired results for that condition. Essential criteria are based on the best available scientific evidence of efficacy in diagnosis and treatment. They may also be derived from the application of a basic principle. For example, the prerequisite for rational antibiotic therapy of a severe infection is identification of the causative organism, or, in urgent situations, taking the appropriate specimens before starting or modifying antibiotic treatment.

The ideal criteria for an audit are purely *scientific criteria* derived from results of randomized clinical trials (RCT), but these are few and far between.[24] One example is the RCT of length of stay for patients with uncomplicated myocardial infarction.[25] Findings in this study showed that the clinical and functional results in patients in hospital for only 14 days are no different from those of patients in hospital for 21 days. Other examples of scientific criteria are those based on the results reported by the Veterans Administration Study Group on Antihypertensive Agents.[26] Lowering the diastolic blood pressure of certain patients to specified levels significantly reduced

TABLE 3.—*Professional Standards Review Organization Definitions of the Three Basic Types of Criteria*[30]

PSRO Term	*Type of Criteria*
Norms	Statistical
Standards	Normative, type unspecified
Criteria	Normative: general consensus or essential Scientific

the incidence of serious or fatal complications in those patients. The data on reduced morbidity and mortality stand as scientific evidence of efficacy of lowering the blood pressure.

Efficacy is what criteria for audits are all about. Scientific study establishes the degree of efficacy or effectiveness of drugs, treatments or operations in reducing mortality, preventing complications or objectively improving the patient's condition. Unfortunately, all this information is not assembled or published in a form that permits audit committees to pick out prespecified "scientific criteria." Instead, clinical experts must be relied on to identify the relatively few items that constitute essential criteria for therapy and the results of therapy.[6,10,27] Experts do this fairly quickly because they limit the criteria in their area of expertise to those that can be supported by scientific evidence.

Many commonly used surgical and medical treatments have not been shown to be effective, and there is a growing challenge to the profession to submit them to clinical trials.[24,28] As this is done, and biomedical and clinical research continue to yield more proven therapies, the scientific bases for criteria will grow. Medical auditing will then expedite the incorporation into hospital practice of the effective innovations and modifications derived from sound clinical research.

One other consideration now enters discussions of criteria—namely, recent rulings on standards of reference in malpractice suits. Historically, courts have admitted expert testimony under the principle that a physician's performance should be compared with that of his peers in his own community. But in 1968 the Brune-Belinkoff decision established the precedent that competence be judged by national standards.[29] The same standards apply to physicians in San Francisco and Baltimore alike. The basis for this ruling is the recognition that scientific criteria of care are generally applicable, without geographic variation. For example drug dosages do not show a regional variation, nor do the results of reducing diastolic blood pressure.

The adoption of essential or scientific criteria makes it mandatory that the audit committee define every instance of nonadherence as an important deviation. As proposed by the JCAH, anything other than 100 percent adherence to essential treatment, in the absence of an adequate justification, calls for peer review.[2] It is inappropriate to set arbitrary expected performance levels when using essential criteria. However, when criteria are selected by general consensus, the threshold for corrective action has to be set at some mutually agreed upon level below 100 percent because there is usually no objectively established relationship between the processes incorporated in the criteria and actual patient results.

PSRO Definitions and Guidelines for Criteria

The National Professional Standards Review Council has adopted different terms for the three types of criteria, and the accompanying definitions are potentially confusing.[30] As shown in Table 3, the Council refers to statistical criteria as "norms." The QAM Report of PAS has adopted this definition and refers to the 25th to 75th percentiles of its national statistics as "norms."[14] But, as discussed above, statistical criteria are only averages. Although useful to some extent in analyzing length of stay, they cannot be construed as acceptable "norms" for purposes of evaluating quality of care.

PSRO refers to normative criteria as "standards" but the manual also states that "criteria" are derived from professional expertise and professional literature. If the criteria are derived from expert professional judgment, they can be essential criteria, based on the best available scientific evidence of efficacy. However, "professional judgment" can also be the basis of optimal care criteria, which are not suitable for evaluating the technical quality of care. Similarly, "professional literature" may refer to results of soundly conducted clinical research (scientific criteria), or to expert opinion (essential criteria) or to general consensus.

These overlapping meanings can mislead some PSRO's into adopting statistical or general consensus criteria for their audits. If so, these PSRO's would inadvertently be maintaining and reinforcing the status quo of care even though their original intent might have been to raise the quality of care.

It is therefore fortunate for the PSRO program

and for medical auditing in general that the American Medical Association's Task Force on Guidelines of Care for PSRO's realized the importance of the fundamental distinction between optimal care (general consensus) and essential criteria. Its first report was illustrated by several lists of the former but it offered no clear statement on their proper use.[31] Subsequently, the Task Force did an about-face: it endorsed critical or essential criteria and cogently defined their rationale and proper use.[32] Everyone concerned with medical auditing should set aside time to study these two reports side by side. This comparison will make clear the necessity to use essential or critical criteria in medical care evaluation studies directed to quality assurance.

"Process" and "Outcome"

Critics of "process" criteria still argue that the only valid basis of assessing medical care is the "outcome." Three things need to be said about this. *First,* just about everything a physician does in the care of his patients (process) can have either the desired positive effect (that is, a beneficial outcome) or a negative effect (that is, a detrimental outcome).[33] *Second,* essential, scientific or critical management criteria are process criteria which are predictive of outcomes that may be immediately observable or long-term and not apparent for one or more years. Examples of the former are the rapid clinical recovery from properly managed nonmalignant intestinal obstruction or from diabetes with ketoacidosis. Examples of the latter are control of diastolic blood pressure in severe hypertension and internal fixation of a hip fracture. *Third,* and most pertinent to this discussion, outcomes cannot properly be included in an audit unless they are directly attributable to medical care (process) received in the hospital.

Viewed in this light, the tiresome arguments over "process versus outcome" are irrelevant. Any process included in an audit must be related to predictable and objectively definable outcomes, and any outcomes that are examined must be directly caused by specified procedures. Therefore, essential criteria for *both process and outcome* must be specifiable for any audit. In practical terms, most outcome audits address preventable or treatable complications of the disease or of its surgical or medical treatment. If such are found in a higher proportion of patients than reported in the best available clinical studies, the causes of the unacceptably high rates can then be discovered by applying essential (critical management) criteria to the steps taken for the prevention and management of those complications.

This approach was proposed by Williamson and subsequently adopted by the JCAH Professional Evaluation Procedure (PEP) program.[2,10] Even though touted as an outcome audit, PEP must limit itself to immediate outcomes caused by efficacious medical care received in the hospital. If clinical experts cannot specify essential process criteria (that is, no effective treatment exists), the topic is not suitable for an audit whose purpose is to evaluate physician performance, no matter what the analysis of outcomes shows.

With the growing awareness of patient compliance as a determinant of proper management following discharge from hospital, results of patient education are now being proposed as legitimate, immediate outcomes of hospital care. These would define how well the patient should know and understand his or her own condition and his or her own responsibilities for continuing self-care after discharge. At present, the methods for specifying and collecting such information in a dependable, useful and acceptable manner are not yet sufficiently refined for general adoption. The importance of documenting this information in selected situations seems clear.[34]

Continuing Medical Education

In the past 20 years, the profession's own initiatives and governmental and societal pressures have combined to firmly establish CME as the third major segment of medical education for the purpose of improving medical competence and medical care.[5] The State of California has joined other states in a growing trend to enact legislation which requires participation in CME as a condition for the reregistration of the medical license.[35] All of the 22 specialty boards of the American Board of Medical Specialties have endorsed the principle of periodic recertification. Ten have set target dates and two already offer examinations. This is powerful voluntary peer pressure to engage in self-education in order to maintain certification. The overall situation amounts to mandatory continuing education, stemming from the belief of organized medicine and state legislatures that CME assures better medical care.

This belief has an obvious justification in the fact that it is impossible to remain abreast of new knowledge and techniques without an organized effort in continuing self-education. And the litera-

ture does contain many reports of improvement in medical care attributable to CME or simply feedback of information indicating substandard performance.[7,10,15,16,34,36,37] Donabedian has compiled some of the previously unpublished reports to this effect.[38] But careful sifting of this literature for hard data leads to the surprising discovery that CME has seldom been reported to change physician behavior promptly or substantially.[36,37,39-42] A national symposium in 1975 described the scope and rationale of CME at length but presented few data on its effectiveness.[43]

CME is now generally believed to be more effective when directed to specific problems in patient care pinpointed by the audit. This is the well-known bi-cycle model.[9,44,45] Both JCAH and the PSRO program endorse this approach.[2,46] But here again, published reports raise questions concerning the effectiveness of the bi-cycle approach in improving physician performance. For example, Table 4 lists the results of serial medical audits in the hospital in which the bi-cycle approach was first developed and applied.[36] Note that in two years, CME produced approximately 50 percent improvement in each of three deficiencies found by audit. One has to wonder how many patients who passed through that hospital during those two years continued to receive the substandard care that had been identified by the first audit. One also has to ask whether the attending staff was really motivated to do something about the deficiencies; they may not have considered them particularly important.

TABLE 4.—*Improvement in Specific Deficiencies Following Application of Bi-Cycle Model in One Hospital*[36]

Deficiency	*1966 Percent*	*1967 Percent*	*1968 Percent*
Complication rate following hysterectomy	25	21	13
Pathology report inconsistent with acute appendicitis	45	37	19
Inappropriate use of antibiotics	70	52	40

TABLE 5.—*Initial Physician Performance Index (1968) and Changes Following Two Years of Continuing Medical Education and Other Efforts to Improve Performance (1970-1971)*[16]

Condition	*1968 Percent*	*1970 Percent*	*1971 Percent*
Acute urinary tract infection	63	67	60
Chronic urinary tract infection	43	54	53
Chronic cholecystitis	68	76	66
Acute cholecystitis	75	79	89
Cancer of breast	67	79	78
Chronic heart disease	61	64	69
Cerebrovascular insufficiency	52	59	60
Cerebrovascular accident	50	55	56
Average	58	66	65

Payne has described the results of his two-year effort to improve physician performance by CME and other means.[16] Shown in Table 5 are the changes in physician performance index for eight diagnoses in one hospital. The improvements are uneven and not at all impressive. Similar disappointing improvement has been described at an academic center.[47]

What are the possible explanations for these results which are well below expectation? Apparently, some physicians look upon CME as an educational exercise, somehow divorced from their actions in treating patients. An illustration of this occurred in a community hospital in which medical audit showed that the medical staff failed to properly followup almost 90 percent of major laboratory abnormalities.[45] Having agreed that this was highly unsatisfactory, the staff requested an educational conference directed to the documented shortcomings. Most of the medical staff participated and afterwards enthusiastically rated it as one of the best CME sessions they had ever attended. But as shown in Figure 1, their level of performance did not improve following the "successful" CME conference.

A second explanation is that a physician's knowledge is not necessarily related to his actual performance. In the study referred to in Table 4, most of the physicians who were prescribing antibiotics inappropriately in a large proportion of their patients showed by written test before the CME effort that they already knew how to use antibiotics appropriately.[36] Another report directly compared the level of knowledge and its application.[48] In this study, 133 patients were evaluated by a team of physicians using a protocol. In 18 patients they diagnosed chronic urinary tract infection on the basis of positive urine cultures. When these same 133 patients were examined in the medical clinic by clinical faculty members and senior medical students (with neither knowing of the prior evaluation), in only eight were positive cultures found. On two objective written tests, the physicians and students who missed more than half the diagnoses showed that they had above-average knowledge of how to recognize and treat chronic urinary infection. There was no consistent relationship between the scores on the test and actual performance in identifying patients with urinary infections.

In the absence of alternatives, CME must remain the foundation stone of professional commitment to maintaining competence. But we should face up to some of its serious limitations. Specifically, CME cannot be relied upon to remove deficiencies in performance when the physicians in question already possess the necessary knowledge and simply do not apply it. Also, it is possible that those physicians most in need of CME are not able to attend conferences designed specifically to assist them in better understanding the reasons why a change in their performance is desirable. Then there is the observation that many physicians who are not providing adequate care nonetheless believe they are keeping up with new developments and feel no need for CME.[49] And finally, it is a well documented fact that on the average, with advancing age, physicians devote less effort to CME, demonstrate less cognitive learning and perform at a lower level.[41,45,49-52] Physicians under 40 years of age do more in CME and achieve better results on tests and in practice than those past 60, on the average. Taken together, these considerations support the conclusion that CME may well be least effective in those who most need it.

Many physicians now hold such a view. In an opinion poll of its members by the California Medical Association, 53 percent of respondents favored the concept of recertification, but only 6 percent would base this on "credit for CME."[53] In contrast, 39 percent favored objective evaluation of clinical performance as a means of determining continuing competence. Among the professional societies, the American Society of Internal Medicine has adopted the position that assessment of physician competence should be based on his day-to-day performance, not "hours of CME" or scores on a written test.[54] But such assessment is as yet neither technically adequate nor logistically feasible. This brings us full circle, back to the central question: what can be done to make the audit and CME more effective in assuring the technical quality of care?

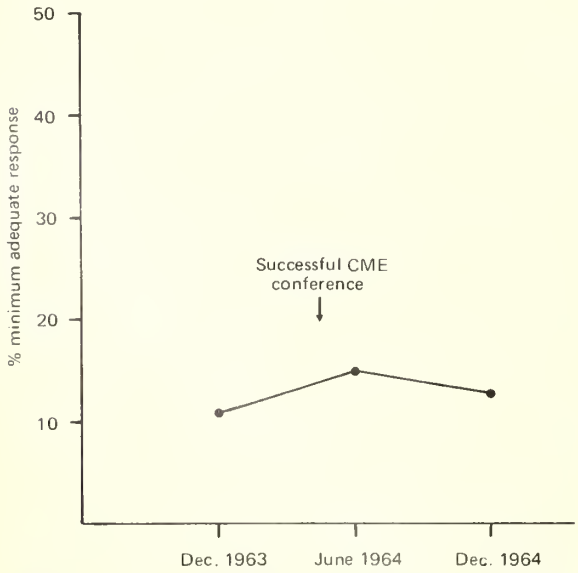

Figure 1.—Percent of minimum adequate responses to abnormal test results before and after continuing medical education (CME) conference.[45]

Quality Assurance

Despite the rapid growth of medical auditing and CME, criticisms of the adequacy of self-regulation in assuring the quality of care persist.[55-60] Stories in newspapers and magazines highlight peaks and valleys in the levels of quality. The continuing publicity given total health care expenditures and the emerging social and political policy goal of equity in health care are forcing a fundamental change in perspective. No longer is it sufficient that physicians have proper credentials and that hospitals be accredited. Even documenting that "on the average" the quality of care is "good" is no longer good enough. Quality assurance is now interpreted increasingly as a near-guarantee that the actual care given every patient meets the prevailing standards of quality. This is the emerging reality within which we must judge the present adequacy of medical auditing and CME.

This position conflicts with commonly stated principles that have helped overcome physician resistance to auditing. For example, hospital-based audit is still promoted in some quarters as an "educational audit" depicting "patterns of care" by "monitoring group performance." In the minds of most physicians, the audit is not intended and should not be used to examine the performance of individual practitioners. Reassuring as they may be, these premises are losing their validity in today's climate of public accountability. And although the profession has adopted CME as the best method of improving performance —by responding to "educational needs" found by audits—an impartial critic would have to conclude that CME, in and of itself, has too little effect on practice habits to be the mainstay of professional self-regulation of quality.

Factors That Improve Performance

To better understand how medical auditing or CME, or both, can better contribute to quality assurance, it may be instructive to consider four circumstances under which the technical quality of care has been shown to improve impressively. These observations point to specific steps that can be taken to raise the level of performance.

In England, surgeons at one hospital were asked to provide certain items of diagnostic clinical information to a team of investigators studying computer-assisted diagnosis.[61] Examination of hospital records for the six months preceding this study showed that 40 percent of patients in whom there was a diagnosis of acute appendicitis came to operation with perforation or abscess. During the same period, in almost 30 percent of the patients with nonspecific severe abdominal pain in whom laparotomy was carried out, there were no positive findings at operation. The actual study lasted 19 months, during which time the surgeons provided the requested clinical data on each patient before deciding whether or not to operate. As shown in Figure 2, the rates for perforation or abscess and for negative findings on laparotomies decreased dramatically. The mere requirement that they provide systematic, critical clinical data apparently enabled the surgeons to improve their diagnostic skills and surgical judgment. The result was that serious, unnecessary morbidity was prevented in most patients with acute appendicitis, and patients were spared more than half the unnecessary exploratory laparotomies for undiagnosed severe abdominal pain. But even more remarkably, four months after the study ended the rates had begun to revert toward the initial unnecessarily and undesirably high levels. The failure to sustain the much improved level of quality of care was not explained. It was established that there had been no change in policy, procedures, staff or equipment.

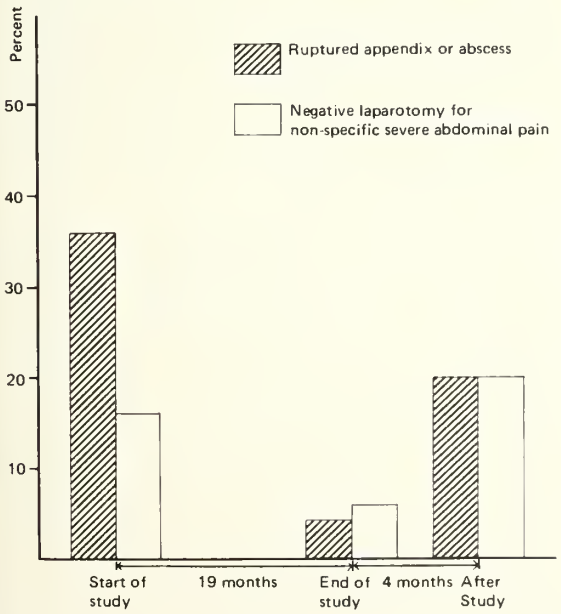

Figure 2.—Changes in frequency of ruptured appendix or abscess and of negative laparotomies during and after study of computer-assisted diagnosis.[61]

Another factor shown to improve performance was the preparation of a protocol to guide physician's assistants and nurse practitioners in diagnosing and treating in patients presenting with acute sore throat.[62] Unexpectedly, when the protocol was put into use, the performance of physicians also changed greatly in the desired direction, as shown in Table 6. Both the rigorous exercise of developing essential process criteria for the protocol and its continuing availability influenced the physicians to improve their recording habits and their treatment patterns substantially.

TABLE 6.—*Physician Performance Before and After Introduction of Protocol for Evaluation and Management of Patients with Acute Sore Throat*[62]

Items of Performance	*Before Protocol Percent*	*After Protocol Percent*
Essential history recorded		
rheumatic fever	1	97
drug allergy	7	94
dysphagia	8	100
Throat culture performed	79	90
Complete blood count ordered	27	14
Antibiotics given	57	18

TABLE 7.—*Effect of a Computer Alert on Physician Performance*[63]

Indicated Change and Reason	*Proportion of Indicated Changes Made by*	
	Physicians Alerted by Printout	*Physicians Using Regular Records*
Reduce aspirin because possible cause of bleeding	2/5	1/5
Reduce triamterene, KCl because serum K>5 mEq/liter	2/3	0/6
Adjust cardiac glycosides and K-wasting diuretics because serum K<3.5 mEq/liter	4/8	0/6
Increase antihypertensives because of undertreatment	8/14	0/7
Reduce thiazides because uric acid>9 mg/dl	2/7	..
Percent of indicated changes made by physicians	49	4

Similar observations were reported when protocols were prepared for determining whether treatment prescribed in a clinic was insufficient, excessive or dangerous.[63] One group of clinicians received computer printouts that alerted them to the possible existence of these situations and suggested the appropriate responses, as defined by the protocols. The changes in treatment made by these clinicians were compared with those of a control group who received no such warnings while caring for similar patients. As seen in Table 7, a much higher proportion of indicated changes was made by those who received computer alerts. The explanation offered is that these warnings focused the clinicians' attention on a particular problem, forcing an explicit decision to continue the treatment or modify it, if in his judgment the situation so warranted. In the absence of such a warning system, many of those using the usual record apparently overlooked the potential danger signals. Assuming that the protocols for the suggested changes were valid, their use substantially improved the care of patients, increasing the likelihood of therapeutic benefit and reducing the risks of serious complications.

A third documentation of sharp change in staff performance was provided by Lembcke in his classic report.[1] Conducting a medical audit at regular intervals in a hospital, he analyzed records to ascertain the number of unnecessary or unjustified pelvic operations. The results were reported in summary form to a joint liaison committee representing the medical staff, board, and administration, but the identities of various surgeons were not given. The "president of the medical staff, assisted by the physician members of the joint liaison committee, interviewed the surgeons with poor individual records and sought their compliance." As shown in Figure 3, there was prompt and striking reduction in the number of unnecessary operations. The criteria were then distributed to the staff near the end of the fourth audit period, and further improvement occurred. This illustrates the impact of a unified, genuine commitment of the staff, administration and board to improve the quality of care, once the precise deficiency and those responsible for it have been objectively and systematically identified by audits based on essential criteria. *This commitment is clearly the sufficient condition for transforming audits, with or without CME, into powerful and effective instruments of quality assurance.*

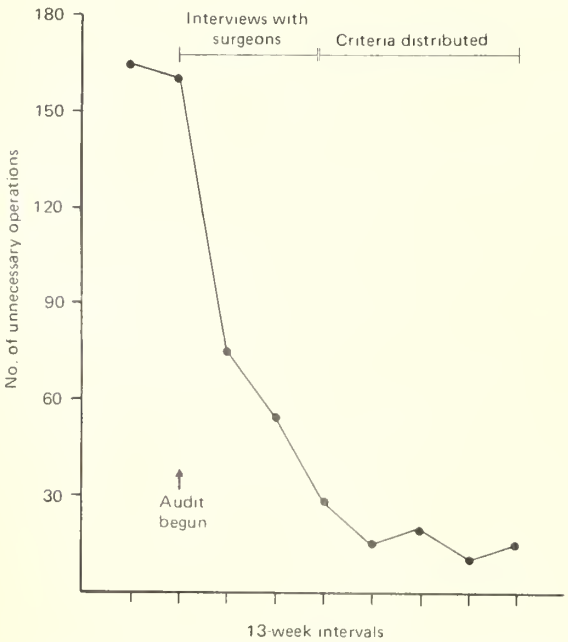

Figure 3.—Effect of interviews and of distributing criteria on the number of cases of unnecessary operations.[1]

A fourth factor known to be associated with a higher quality of care as reflected in physician performance is a teaching environment.[64-68] The precise mechanisms which lead to better results have not been documented, but it seems that the teaching environment sets and maintains high expectations for the level of actual performance. For example, Stapleton observed that physicians ordered critical tests more frequently on the teaching than on the nonteaching wards of a hospital.[64] In the New York studies, there was no real difference in quality of care attributable to certification or noncertification of the physicians, but care was superior in hospitals affiliated with a medical school.[65,66]

One obvious common denominator in the studies described above is a professionally acceptable form of surveillance or monitoring. Each of the techniques for monitoring achieved that which is impossible for CME: each influenced the physician at the *time and place he was actually providing care to an individual patient.* Acting directly or through enhanced awareness and motivation, each of these assisted the physician in applying more fully the information and skills that he already possessed.

The Public Trust and Quality Assurance

It is natural for physicians to look at auditing primarily from the standpoint of its possible im-

plications for the physicians' status in that hospital, rather than its implications for patients' welfare. Yet, a hospital's obligation is to its patients. Its corporate legal responsibility calls for much more than passive concern over those patients about to be admitted to the hospital who will suffer unnecessary complications or deprivation of full benefit unless measures are taken to eliminate the deficiencies identified by audit.[29,58]

Corporate responsibility requires active and prompt correction of those deficiencies, followed by a suitable form and frequency of monitoring to assure that all patients are actually receiving the proper treatment and the expected results.[2] This is the quality assurance cycle. The extent to which audit and CME will be judged to serve the public trust adequately will be in direct proportion to their proven effectiveness in making that cycle a reality.

An Organized Program of Quality Assurance

The present review of the medical audit indicates that it is not an all-purpose technique for assessing all important aspects of the technical quality of care. The present state of medical science is such that rigorous auditing can only be applied to a narrow segment of patient care. Therefore the full burden of professional monitoring should not rest on the medical audit committee(s) alone. Quality assurance requires an organized program encompassing the activities of all hospital and staff committees that bear on quality. These include departmental review committees, plus transfusion, infection, tissue, death and complications, emergency room, pharmacy or drug, and record committees, in addition to the audit and utilization review committees.

There are advantages in coordinating all such quality-related committee work. The individual committee reports, combined with the cumulative results of audits, add up to a comprehensive documentation of all aspects of the quality of care. That documentation serves as a solid base of due care by the medical staff and board in regularly and objectively assessing how well each physician is discharging his obligations in exercising the clinical privileges granted him by the hospital. In this problematic and too often imperfectly and inadequately executed judgment, medical audits can play a vital role, if designed to yield valid comparative information on staff performance in important areas of care. Corrective action, when indicated, can be initiated promptly with fuller understanding of the scope and sources of deficiencies that are to be remedied. In less urgent situations, CME, if properly prescribed, may suffice. Depending on local resources and interests, other approaches as described above can be initiated to raise to standard levels some specific aspect of the quality of care.

The continuing upsurge in public demand for accountability in quality is probably irreversible. In responding, the medical staff and hospital administration have one unassailable professional position: commitment to assuring every patient of full achievable benefit at least possible risk. This commitment is the cardinal prerequisite for quality assurance in its fullest contemporary meaning. In such settings properly designed medical audits and CME will be effective in improving physician performance.

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Informed
OPINION

Refer to: Butler JR Jr: Arbitration agreements and your malpractice coverage (Informed Opinion). West J Med 125: 253-258, Sep 1976

Arbitration Agreements and Your Malpractice Coverage

JAMES R. BUTLER, JR., Esq., *Beverly Hills*

With new legislation and favorable case law developments, many providers of health care services are turning to binding arbitration agreements as a partial solution to the medical malpractice crisis. Existing data indicate tremendous advantages can be gained from the use of such agreements, if they are carefully drawn to comply with new law, tailored to the particular situation in which they will be used and coupled with appropriate procedures to secure the intended benefits.

Arbitration is not a substitute for insurance, but if a provider has taken the calculated risk of forgoing insurance he should not be without a carefully drawn binding arbitration agreement.

While the hue and cry of the medical malpractice insurance crisis continues to ring in newspapers and magazines, many less emotional but more calculating health professionals are taking aggressive steps to lower their own insurance rates. Their stratagem is the adoption of office or institutional procedures requiring each new patient, as a condition to treatment, to sign an agreement to binding arbitration of disputes. The best of those agreements generally contain provisions for payment of costs and attorneys' fees by the losing party and bonding requirements to secure payment of such costs and attorneys' fees.

The solution forged by these pragmatic physicians, lawyers and health managers has enabled them in some cases to reduce insurance rates while at the same time decreasing the likelihood that they will become embroiled in vexatious litigation. This has important psychological, emotional and economic effects on the physician-patient relationship.

Arbitration Is Not Compromise

While the term "arbitration" connotes "compromise" in the minds of many nonlawyers, arbitrations in the health field have often resulted in fully vindicating victories for providers. In Southern California, for instance, a pilot project originally involving eight hospitals has achieved dramatic early success. Although in practice for only about four years, the arbitration process has resulted in decisions for the defense in all four cases decided. Furthermore, it appears that these hos-

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Editor's Note: A booklet "Arbitration for Physicians in Private Practice" published by the California Medical Association is available free to CMA members and at a cost of $1.00 per copy to others. The address for requests is: Sutter Publications, Inc., 731 Market Street, San Francisco, CA 94103.

pitals have been experiencing slightly less than average claims incidence. Other groups adopting arbitration include The Kaiser Foundation Hospitals, Southern California Permanente Medical Group and Ross-Loos Medical Group. The latter has the most extensive experience with contractual arbitration for resolving medical malpractice disputes. Ross-Loos adopted binding arbitration shortly after its founding in 1929 and therefore has years of experience with the approach. The Commission on Medical Malpractice examined the Ross-Loos experience[1] and found that approximately 95 percent of the claims were settled informally without the necessity of going to arbitration. They found that the time required to settle claims was considerably less than the time required for court cases, and costs of plaintiffs and defendants were only 55 to 85 percent of costs for comparable claims in lawsuits (exclusive of awards to plaintiffs).[2]

Background

In the face of the increasing number of malpractice claims made each year, the increasing size of jury-awarded malpractice recoveries, rising malpractice insurance costs (more often labeled "skyrocketing") and the complete withdrawal of some insurance carriers from the field, every provider of health care services must consider the value of a properly drawn arbitration agreement. In obtaining the desired benefits, it is essential that arbitration not be implemented through the blind use of rote forms. Moreover, developments in the field have been so rapid that uninformed counsel may be totally ineffective. In California, for instance, most arbitration agreements currently in use became fatally defective and unenforceable when new legislation (AB1—the Keene Bill) became effective on December 12, 1975. Knowledgeable counsel must tailor an arbitration agreement to fit the unique requirements of each office or institution.

Arbitration Discourages Nuisance Claims

The existence of an arbitration agreement may act as a deterrent to nuisance claims. There appears to be something inherent in the arbitration process that discourages medical malpractice claims; and, a properly drawn arbitration agreement may now place additional significant obstacles in the path of a "nuisance claimant." The magnitude of the "nuisance" claim problem was shown in the Secretary of Health, Education, and Welfare's medical malpractice report.[3] It stated that of the 16,000 malpractice cases closed by insurance companies in 1970, half were closed before a lawsuit was begun, and only a quarter of the cases resulted in the claimant receiving a financial settlement. Of the 8,000 actual lawsuits, 80 percent were settled out of court and in 60 percent the claimant received some payment. Only 20 percent of the lawsuit cases ever came before a jury, but the verdict was in favor of the physician in four out of every five of them. Only 3 percent of the cases were settled for or awarded sums of more than $100,000 and more than half the claimants received less than $3,000—probably not enough to cover legal costs.

While all small claims are not brought to extort a nuisance settlement from a provider, there can be no doubt that a significant percentage of the increase in the number of malpractice claims made each year are apparently "nuisance" claims. The reason is easy to understand. Basically, if there is any colorable ground for a claimant to assert malpractice (whether because of disappointed expectations, failure of physician-patient communications or some similar reason) a plaintiff's lawyer is well aware that the costs of answering and defending such a claim are enough to create great pressure on the provider and the insurance carrier to pay a few thousand dollars—regardless of the claim's substantive merit. The tremendous leverage that unscrupulous claimants and their attorneys have is shown by the fact that most insurance carriers find that their costs of defending actions are at least equal to the total amount of claims payouts. The courts simply make vindication of an innocent provider too expensive.

Anything, then, that can be done through arbitration to discourage nuisance claims must have a beneficial impact on the medical malpractice crisis. In this regard, a startling fact has emerged from an analysis of the Ross-Loos Medical Group experience.

Since 1964, that group has had approximately 35 claims made, all but three of which were settled before arbitration.[4] During the same period there were 36 cases that were filed in Superior Court against the group and then stayed because of the arbitration clause in the subscriber agreement. Subsequently, 23 of the cases were dropped by the plaintiffs. The apparent abandonment of those cases led one expert to comment as follows:

"What is there about arbitration that made

these attorneys 'roll over and play dead'? Others involved with binding arbitration have noted the same tendency."[5]

There may be a number of reasons that will explain this. Some trial attorneys may simply find the unfamiliarity of an arbitration forum too forbidding. Others may find that their talents in recovering for their clients and earning a contingent fee for themselves are best applied before juries where techniques of persuasion, as opposed to marshaling of facts, can be given the greatest premium.

Additional Impediments to Nuisance Claims—Carefully Drawn Provisions

In addition to any factors inherent in the arbitration process, imaginative and carefully drawn provisions in the arbitration agreement can further discourage "blackmail" claims. In a court suit, a nuisance claim may be instituted with minimum costs, basically the filing fee for a complaint—which in Los Angeles County is approximately $50. By contrast, use of the arbitration process can increase the actual costs a claimant must bear to get his claim on file in order to pursue his remedy. Rather than pay $50 for a possible $2,000 recovery, some of which would go to his attorney, he may be required to make an investment of $500 to $1,000 for the same kind of recovery (which he will get back only if he prevails). Furthermore, with a properly drawn arbitration agreement he may be liable for additional costs if he does not prevail. Now the risk-reward ratio begins to tip the other way.

An illustration may be helpful. Suppose a provider required each patient to sign an arbitration agreement with the following provisions:

- The prevailing party is entitled to recover *all* of its out-of-pocket costs, including filing fees, attorneys' fees, arbitrators' fees and other such items.
- The initiating party in a dispute must post a bond to provide security for costs if he loses. Since the security for costs is refundably only upon victory, no bonding company will post the bond for less than 100 percent of the face amount. Therefore, the liability for commencing an arbitration proceeding would be the $150 filing fee plus a reasonable bond, probably around $500, for a total of $650 (compared with $50 for commencing a lawsuit as explained above).

These provisions, which must be expressly set forth in the agreement, consequently raise the "front end" cost to a claimant initiating an action as well as the total cost if he is unsuccessful. An attorney is prohibited from paying such out-of-pocket costs for his client, even in a contingent fee case, by the American Bar Association and State Bar Canons of Ethics. For a claimant with a legitimate grievance, the differences in cost will not provide any significant deterrent. However, both the nuisance claimant and his attorney must make a new assessment of their potential exposure.

Although this formula has not been completely tested, the worst that can happen is that the matter will be tried in a court of law. However, the courts have repeatedly indicated a strong public policy favoring arbitration agreements. The California Supreme Court in the case of *Doyle v. Giuliucci* upheld the Ross-Loos binding arbitration arrangement against the plaintiff's attack that it was a denial of the constitutional right to a jury trial. The court stated that it merely provided an alternative forum to resolving the dispute. In California, furthermore, the Keene Bill settles for all time the enforceability of agreements complying with its strict standards. Authority for requiring security bonds for costs is not new either. California and other state statutes may require security in libel and slander suits and in derivative suits by corporate shareholders.

A note of caution must be sounded about the approach taken in drafting such agreements. Arbitration provisions should not be so onerous as to completely deny access to an alternative forum—a mistake which could void the whole agreement. For example, the face amount of the security bond should not be unreasonably high. To be completely safe, a severability clause should be inserted in the contract so that if one provision is found unenforceable, the remaining advantages of arbitration still will be available to the providers.

Arbitration Is Faster

Another important benefit of arbitration is that it generally leads to a quicker resolution of disputes. A detailed study has found that the average time from the incident of a malpractice claim to resolution through settlement or litigation in the courts ranges from three to five years, depending upon the approach used in reaching a settlement.[6] Actions at law requiring a jury verdict take an average of five years to settle, with 10 percent of the cases to be decided by a jury still pending

after six years and ten months. In fact, it takes ten years to resolve all malpractice claims arising in any single year.[7] By comparison, one study found that the average time to final resolution of a dispute through *arbitration* was less than three months, and that appears to be confirmed by the Southern California Hospital Association's pilot arbitration project which has experienced an average time of three to six months. Obviously, certain cases may run much longer depending on the case complexity and need for discovery, but averages are more instructive than exceptions.

One interesting side effect of speedy disposition of disputes through arbitration appears to be a greater pressure to settle. A national study found that 65 percent of all court cases settled before trial, and most settlements were on the eve of the trial itself.[8] A study of the binding arbitration system utilized by Ross-Loos in Los Angeles indicates that over 95 percent of all claims made since 1964 (the earliest date for which files are still available) were settled before the arbitration hearing.[1] This led one special study group to comment:

"Many defenders and supporters of arbitration believe that the arbitration process itself creates a unique psychological incentive for achieving settlement prior to actual hearing. They note that the more immediate deadline that accompanies an arbitration proceeding creates this incentive which is lacking in prolonged and delayed litigation processes."[9]

For the provider—particularly if he is wrongfully accused or being "blackmailed" with a nuisance suit—the inordinate amount of time required to resolve a medical malpractice claim is distressing. Such claims represent contingent liabilities which must be disclosed on a balance sheet. Whether or not such disclosures actually impair a provider's ability to conclude a business transaction, many of our provider clients have found it frustrating and embarrassing to "explain" these items, particularly when they feel the claims are without merit or that the dispute will actually be settled within the policy limits of their medical malpractice insurance.

Arbitration Is Cheaper

Many times a collateral benefit of such programs derives from the fact that arbitration is generally less expensive. The apparent reasons for these cost savings in resolving disputes through arbitration must include elimination of nuisance claims; speedy resolution of disputes through settlement before the arbitration, and elimination of technical rules of pleading and evidence which give rise to time-consuming and expensive objections, arguments, hearings and briefs, and necessitate elaborate procedures and strategies in order to produce a case that might otherwise be presented in a more straightforward fashion. A court trial which typically requires from three to eight days can usually be completed in arbitration in six to eight hours. That time saved at the hearing stage alone results in lower attorneys' fees, court costs, reporter costs and other attendant fees.

It is undoubtedly the significant economies that appear to be emerging from the use of arbitration that have led legislatures, insurers and providers all to turn increasingly to arbitration as one element of the solution to the current medical malpractice crisis.

Arbitration Uses Experts

An interesting element of arbitration is the choice of panel members. The arbitration panel will be as sophisticated as the contractual mechanism provided for selecting it. An arbitration agreement can permit the use of a highly knowledgeable and competent decision maker as opposed to the typical jury which may be more susceptible to emotional appeals. For example, the American Arbitration Association utilizes a panel of three arbitrators composed of one lawyer, one businessman and one person from the field of health if the claim exceeds $20,000. Most authorities agree that even corporate lawyers or businessmen can make a far better reasoned judgment in a medical malpractice dispute than a jury because their training teaches them to evaluate data and reach decisions upon logical bases rather than upon sympathetic association.

Arbitration Awards Are Reasonable

Another matter of concern to the provider, the patient and the insurer is the size of the award which an expert or sophisticated tribunal is likely to make. On this question, Frederick O. Field, legal counsel for the Los Angeles County Medical Association, commented on the ability of juries to handle cases involving medical malpractice:

"Juries often do not know how to evaluate the medical results. A lawyer that can present a deformed child to a jury and argue that the obstetrician made a mistake in prescribing a drug for

the mother has a strong emotional argument for him.

"Even if the physician can bring in 15 specialists who say that the obstetrician did the right thing (the jury) favors the plaintiff . . . because of the powerful emotional argument generated by the sight of the deformed baby."[10]

The obverse of the generalization made by Mr. Field in the foregoing statement appears to be borne out by the Ross-Loos Medical Group's experience. Although this medical group has utilized binding arbitration since 1930, most cases have been settled before the arbitration hearing. In fact, there have been only three claims actually proceeding to arbitration since 1964. In one of these, a decision was rendered for the claimant. Both the award for claimant and the amounts of the award were no less favorable than the result that might have been obtained from a jury trial. However, in the other two decisions, the arbitrators found for the provider and against the claimants. In these two instances, a jury verdict would almost certainly have been rendered for the claimant on a sympathy verdict. The experts evaluating the arbitrations did not in any way find that the arbitrator's decision was unfair. They concluded the arbitrators were simply able to understand complex issues and to decide a case logically upon clearly established legal principles.

In its report mentioned above, the Secretary's Commission on Medical Malpractice concluded:

"Perhaps most important in the field of professional liability is the fact that the arbitration process is a fact-finding procedure conducted without the emotional overtones and adversary atmosphere of the courtroom."[11]

Arbitration Is Private

Lawsuits are, by their nature, very public proceedings. From the time a complaint is filed with the clerk of the court, anyone can obtain copies of the complaint or any other documents filed with the court. Some complaints make rather spectacular reading, and because statements in a complaint enjoy a qualified privilege against libel, there is little recourse that an aggrieved provider can take against an overly zealous plaintiff for contentions that may never be proved, but may be released to the detriment of the provider, to the news media or other persons. In fact, the very trial itself is an open and public proceeding where a skillful malpractice attorney can ask insinuating questions or introduce into the public record facts or circumstances that place the provider in a very unfavorable light. All of these questions or facts may be totally unfair. They may have a perfectly valid "explanation" or be entirely irrelevant to the issue at hand, but juries, reporters and others find sensationalistic smears far more newsworthy than the exculpating explanations required to put events or statements in context and exonerate the victim of the smears. By comparison, arbitration papers and proceedings are not public. While there can be no assurance of secrecy, records and hearings are regarded by the American Arbitration Association as confidential.

Arbitration Decisions Are Final

Statistics indicate that 23 percent of all litigated cases are appealed.[12] In contrast, binding arbitration decisions are virtually unappealable. When the parties have agreed to submit a dispute to binding arbitration, any appeal from that decision is extremely limited. In essence, appeals can be taken from the final arbitrators' decision only on the grounds of fraud and outstanding error.[13] The burden of proof to establish these defects is on the person seeking to overturn the arbitrators' decision, and it is a difficult burden to sustain.

Conclusion

As the malpractice crisis continues, interest in the use of binding arbitration agreements has increased tremendously. In California, new legislation and continuing favorable court decisions have helped to secure to providers of health services the benefits of arbitration. It is something that every provider of health services should seriously consider implementing in his own operations.

Many outdated arbitration forms are still in circulation. Other sample forms have been prepared by various organizations—in California, for example, by the California Hospital Association (CHA) and the California Medical Association (CMA). While many of these samples demonstrate a thorough and thoughtful approach to various problems, by their very nature they cannot be tailored to an individual provider's particular circumstances. As a result, many forms are unduly conservative or overly restrictive and fail to yield the maximum advantages of arbitration to the provider.

For example, the model form suggested by the CHA and CMA is strictly voluntary—the patient is merely requested to execute an arbitration agreement. The agreement expressly provides that a

patient's signature on the form is not a precondition to furnishing of medical services. There is no necessity for this overcautious approach—if the arbitration agreement is carefully drafted and the provider of health services consults with his attorney so that he both understands the necessary procedures, the relative merits and the drawbacks of arbitration proceedings and has a carefully tailored legal document.

Under no circumstances should any provider of health services regard an arbitration agreement as a substitute for insurance. It is not. However, if a provider has decided to go "naked"—that is, to go without insurance—the advantages of arbitration become even more compelling. Although the experience to date has been relatively limited, the results appear remarkably uniform. Binding arbitration has been extremely effective in health services to vindicate innocent providers and compensate the truly injured consumers, while discouraging nuisance claims, speeding up dispute resolution, providing significant economies, employing greater expertise, resolving claims without emotional appeal, providing a private forum for dispute resolution and giving greater finality to a decision, once reached.

The limited experience coupled with new legislation leaves a number of unanswered questions and providers should regularly consult with their counsel as more experience is obtained and as answers are found to unresolved issues raised by the new law. For example, the new law applies to a "contract for medical services"—what is such a contract? How often must an arbitration agreement be signed—every time a consumer requests health care services? Must the agreement set forth the 30-day recision right? Are *all* arbitration agreements validated under *all* circumstances with the new law?

While additional results are being tabulated and as the questions are being answered, it appears providers of health care services have much to gain and nothing to lose in implementing binding arbitration for resolving medical malpractice disputes.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *From time to time members of the Editorial Board call attention to articles in other journals which they consider to be particularly significant. The editors believe these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

The Basis for Amine Hypotheses in Affective Disorders

Baldessarini RJ

Archives of General Psychiatry
32:1087-1093, Sep 1975

DISCIPLINES: Psychiatry, Basic Sciences

READABILITY: Very good

An excellent evaluation of present status of the "amine theories." In the process of judging, the author also reviews and instructs. It is lucidly written with clear sequential logic.

—J. M. STUBBLEBINE, MD
Greenbrae, CA

Abstracts of Papers Given at Annual Meeting of the American Academy of Allergy at San Juan, Puerto Rico, March 6-10, 1976

Journal of Allergy and Clinical Immunology
57:189-266, Mar 1976

DISCIPLINES: Allergy, Clinical Immunology

READABILITY: Excellent

A quick ready reference to what the allergists-immunologists discuss at annual scientific meetings. The 186 very short abstracts should certainly be interesting to all physicians.

—NORMAN SHURE, MD
Los Angeles

A Prospective Study of Drugs and Pregnancy—I. Psychopharmacea

Kullander S, Källén B

Acta Obstetricia et Gynecologica Scandinavia (Lund)
55:25, 1976

DISCIPLINE: Obstetrics

READABILITY: Excellent

A very important article for anyone who prescribes psychic drugs for a pregnant woman. This is an excellent prospective study of the use of psychic drugs in pregnant women.

—RALPH W. HALE, MD
Honolulu

Special Issue: Acne

Frank SB (Guest Editor)

Cutis
17:459-608, Mar 1976

DISCIPLINES: Dermatology, General and Family Practice, Biochemistry, Microbiology, Endocrinology, Pharmacology

READABILITY: Excellent

All aspects of current understanding of the pathomechanism and management of acne are reviewed by some of the leaders in acne research.

—REES B. REES, MD
San Francisco

A Systematic Approach to the Evaluation of Immunological Disease Patterns

Warren SL

Annals of Allergy
36:180-192, Mar 1976

DISCIPLINES: General Medicine, Immunology

READABILITY: Good

A very good review of immunological disease states and the mechanisms involved. Methods and techniques for diagnosis are clearly outlined, categorized, tabled and explained. A good text for the novitiate and a good review for others.

—NORMAN SHURE, MD
Los Angeles

Prenatal Diagnosis of Chromosomal and Enzymatic Defects

Goldstein A, Dumars K, Kent D

Obstetrics and Gynecology
47:503, Apr 1, 1976

DISCIPLINE: Obstetrics

READABILITY: Good

An excellent discussion of the reasons for and against amniocentesis. It handles all of the common problems and controversies. A concise, simple description of their technique is presented, as well as their recommendations. This article is appropriate for all physicians who care for pregnant women.

—RALPH W. HALE, MD
Honolulu

Beta-carotene and the Photodermatoses

Pollitt N

British Journal of Dermatology
93:721-723, Dec 1975

DISCIPLINES: Dermatology, Photobiology, Internal Medicine, Pharmacology, General and Family Practice

READABILITY: Very good

The photodermatoses have diverse etiology, including drug- or chemical-induced, metabolic disease and idiopathic. The discovery that beta-carotene helps erythropoietic protoporphyris had led to the hope that it will help other photosensitive disturbances. The author details the present state of the art.

—REES B. REES, MD
San Francisco

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

DIAGNOSTIC RADIOGRAPHY—A Concise Practical Manual—Second Edition—Glenda J. Bryan, DSR, SRR, Superintendent Radiographer, Bristol Royal Hospitals; Foreword by J. H. Middlemiss, CMG, MD, FRCP, FFR, Professor of Radiology, University of Bristol. Longman Inc., Churchill Livingstone-Medical Division, 72 Fifth Avenue, New York City (10011), 1975. 356 pages, $13.00.

This edition of Glenda Bryan's *Practical Manual on Diagnostic Radiography* introduces new information and new chapters on xeroradiography, thermography, computerized transaxial tomography, and forensic radiography. These are needed and are valuable contributions to the technologist's capabilities. The book is well printed, well proportioned, and the illustrations are excellent. As a textbook, it may be somewhat advanced for most of our technology students, but it reads so well and it is so authoritative that it will make a good manual for accomplished radiographic technologists in this country as well as for radiographers in Britain.

The excellent chapter on patient care and radiation protection does not seem to include the British concern for the potentially pregnant female, but does have excellent paragraphs on consent forms and on the limitations imposed by infants and small children. The section on xeroradiography is overly enthusiastic about the radiation-sparing qualities of xeroradiography and the section on ultrasound seems rather skimpy. These are otherwise minor quibbles about an otherwise fine book which I will recommend to all of my senior technologists.

B. J. O'LOUGHLIN, MD

* * *

RETINA CONGRESS—25th Anniversary Meeting of the Retina Service, Massachusetts Eye and Ear Infirmary. Edited by Ronald C. Pruett, MD, Clinical Instructor in Ophthalmology, Harvard Medical School, Assistant Surgeon in Ophthalmology, Massachusetts Eye and Ear Infirmary, Clinical Senior Scientist, Retina Foundation, Boston; and Charles D. J. Regan, MD, Associate Professor of Ophthalmology, Harvard Medical School, Associate Chief and Surgeon in Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1974. 730 pages, $45.00.

This record of the proceedings of the Retina Congress, convened in September, 1972, to commemorate the 25th anniversary of the Retina Service of the Massachusetts Eye and Ear Infirmary, is fittingly dedicated to its founder and director, Dr. Charles L. Schepens. His former students and their pupils met in Boston with other experts from many parts of the world to review the progress in diagnosis and treatment of retinal diseases in the past quarter century, to assess current concepts and to evolve future investigative and therapeutic methods.

The eighty-five contributors cover a very wide field and their reports contain a massive bibliography. The book is a valuable reference work which should have its place in the library of every ophthalmologist interested in the complex subject of the retinopathies, their etiology, diagnosis and treatment.

The contributors review current basic concepts of retinal anatomy and physiology, and describe modern methods of ocular examination. Fluorescein angiography, ultrasonography, electrophysiology and special photographic modalities are considered. The most advanced methods for the surgical treatment of retinal detachment along with their results and complications are reported. The vitreous body and its relationship to retinal disease is investigated and new methods of vitreous surgery are described.

The historical record of the enormous advances in the treatment of retinal disease in the past twenty-five years gives due credit to Dr. Schepens' development and popularization of binocular indirect ophthalmoscopy. His teachings have revolutionized the science and art of diagnosis and treatment of retinal disease.

The book is well printed and extensively illustrated.

DAVID O. HARRINGTON, MD

* * *

NUCLEAR MEDICINE IN CLINICAL PEDIATRICS—Edited by Hirsch Handmaker, MD, Director, Nuclear Medicine, Children's Hospital of San Francisco; and Jerold M. Lowenstein, MD, Chairman, Department of Nuclear Medicine, Pacific Medical Center, San Francisco. Publishing Sciences Group, Inc., 411 Massachusetts Avenue, Acton, MA (01720), 1975. 296 pages, $22.50.

This book is based on a symposium held in February 1973. It is written primarily for pediatricians who want to know how nuclear medicine procedures apply to their problems. Nuclear physicians on the other hand, can learn to apply these procedures to pediatric patients. Highlights from both areas are well organized into an easily read survey. Although this book is not an exhaustive text nor a reference volume, it is an excellent practical handbook.

Most chapters are concerned with one idea or one organ. The chapters are written by experts who have included clear illustrations and graphs. They report the state of the art accurately.

The last chapters predict progress in new instrumentation, radioactive pharmaceuticals and computers. Most of these new ideas are reasonable but they have not become routine practice in the three years since the symposium was held.

The appendices contain data about sedation, dose and normal values. This information is especially valuable to physicians practicing pediatric nuclear medicine.

FLORIAN W. ZIELINSKI, MD

* * *

CURRENT DERMATOLOGIC MANAGEMENT—Second Edition—Edited by Stuart Maddin, MD, FRCP(C), Clinical Associate Professor, Division of Dermatology, Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver; Drug Consultant: Terence H. Brown, BSP, MS, PhD, Associate Professor, Faculty of Pharmaceutical Sciences, University of British Columbia. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis (63103), 1975. 404 pages, $39.50.

This is the second edition of a multi-contributor text which outlines therapeutic procedures and drugs in the management of cutaneous disease. There are close to 200 contributors and one thereby obtains a wide cross-section of opinions even though each disease entity is covered by only one author. The text is up-to-date and should prove quite helpful as a reference for dermatologic therapy.

A detailed drug index is included in this volume with brief coverage of chemistry, mode of action, absorption, excretion and dermatologic indications for use for the more important compounds to dermatologic therapy. The only criticism of the book would be its lack of presentation of basic principles in pharmacology as related to the skin but this should prove a fairly valuable reference for people in the practice of dermatology, residency training in dermatology, and even for the general practitioner.

RICHARD B. STOUGHTON, MD

in memoriam

ALEXANDER, ALDEN HAY, Redwood City. Died July 2, 1976 in Redwood City, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Dr. Alexander was a retired member of the San Francisco Medical Society.

BERSHAD, SOLOMON, Panorama City. Died May 22, 1976 in Panorama City of glioblastoma, aged 61. Graduate of the University of Cincinnati College of Medicine, 1940. Licensed in California in 1949. Dr. Bershad was a member of the Los Angeles County Medical Association.

CAMPBELL, ROBERT MAXWELL, Sacramento. Died July 6, 1976 near Placerville, aged 62. Graduate of Northwestern University Medical School, Chicago, 1939. Licensed in California in 1949. Dr. Campbell was a member of the Sacramento County Medical Association.

CHAU, SEK-HONG, El Centro. Died July 13, 1976 in El Centro, aged 58. Graduate of the University of Linghan Medical College, Canton, 1943. Licensed in California in 1957. Dr. Chau was a member of the Imperial County Medical Society.

CHRISTENSEN, DALE C., Richmond. Died July 3, 1976 in San Pablo of diffuse interstitial pulmonary fibrosis, aged 64. Graduate of Washington University School of Medicine, St. Louis, 1943. Licensed in California in 1945. Dr. Christensen was a member of the Alameda-Contra Costa Medical Association.

COOK, CARL LAWRENCE, JR., San Bernardino. Died July 17, 1976 in San Bernardino, aged 55. Graduate of Yale University School of Medicine, New Haven, 1946. Licensed in California in 1950. Dr. Cook was a member of the San Bernardino County Medical Society.

CRAIG, JOHN F., Sacramento. Died May 27, 1976, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1936. Licensed in California in 1936. Dr. Craig was a retired member of the Sacramento County Medical Association.

DANNO, SAMUEL PETER, Los Angeles. Died April 20, 1976 in Los Angeles of acute myocardial infarction, aged 66. Graduate of the George Washington University School of Medicine, Washington, DC, 1933. Licensed in California in 1934. Dr. Danno was a retired member of the Los Angeles County Medical Association.

FONG, ROBERT RONALD, JR., Sacramento. Died June 18, 1976 in a light airplane crash near Susanville, aged 43. Graduate of the University of California at Los Angeles, School of Medicine, 1958. Licensed in California in 1960. Dr. Fong was a member of the Sacramento County Medical Association.

GERNAND, HENRY CHRIS, Los Angeles. Died June 24, 1976 in Los Angeles of lung infection, aged 73. Graduate of State University of Iowa College of Medicine, Iowa City, 1927. Licensed in California in 1928. Dr. Gernand was a member of the Los Angeles County Medical Association.

GLYN-DAVIES, ALEXANDER, Santa Monica. Died May 8, 1976 in Santa Monica of bronchopneumonia, aged 80. Graduate of Faculty of Medicine University of Edinburgh, Edinburgh, 1924. Licensed in California in 1950. Dr. Glyn-Davies was a retired member of the Los Angeles County Medical Association.

HASHIBA, GEORGE K., Fresno. Died June 16, 1976, aged 88. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1917. Licensed in California in 1917. Dr. Hashiba was a retired member of the Fresno-Madera Medical Society.

HAWK, MALCOLM H., Palo Alto. Died June 27, 1976 in Sharon, Pennsylvania, aged 68. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1934. Licensed in California in 1938. Dr. Hawk was a retired member of the Santa Clara County Medical Society.

HIGGINS, ALTON R., San Francisco. Died October 16, 1975 of pneumonia, aged 69. Graduate of McGill University Faculty of Medicine, Montreal, 1932. Licensed in California in 1948. Dr. Higgins was a retired member of the Alameda-Contra Costa Medical Association.

JOHNSON, MALCOLM C., Vallejo. Died June 23, 1976 in Santa Cruz, aged 74. Graduate of Loyola University School of Medicine, Chicago, 1927. Licensed in California in 1937. Dr. Johnson was a retired member of the Solano County Medical Society.

LEWIS, LEONARD MARTIN, Santa Monica. Died May 12, 1976 in Los Angeles of cancer, aged 48. Graduate of Loyola University of Chicago, Stritch School of Medicine, Chicago, 1956. Licensed in California in 1957. Dr. Lewis was a member of the Los Angeles County Medical Association.

LOOSLI, CLAYTON G., Los Angeles. Died June 27, 1976 in South Pasadena, aged 71. Graduate of the University of Chicago, the School of Medicine, 1937. Licensed in California in 1948. Dr. Loosli was a member of the Los Angeles County Medical Association.

LOVE, CHARLES A., San Bernardino. Died June 25, 1976 in San Bernardino, aged 82. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Dr. Love was a retired member of the San Bernardino County Medical Society.

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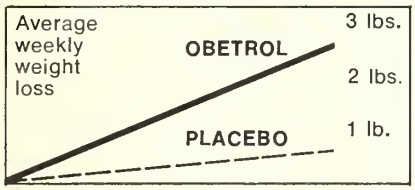

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Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

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2. Minimal brain dysfunction:
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   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

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January 1973

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PHYSICIANS WANTED

PATHOLOGISTS: The Department of Pathology at UCLA is willing to consider applications for appointment to the Clinical Staff on a volunteer basis. Applicants should have expertise in teaching and an interest in participating in the instructional program for the Second Year Medical and Dental Students as well as Interns and Residents of the department. UCLA is an Equal Opportunity/Affirmative Action Employer. Send Curriculum Vitae to J. L. Van Lancker, MD, Department of Pathology, University of California, Los Angeles, Los Angeles, CA 90024.

PRIMARY CARE PHYSICIANS—If you are interested in living in the Pacific Northwest, we may be able to assist you in finding the practice location best suited to your professional and personal interests in Washington State. The Clearinghouse: Community Advocates for Health Resource Development, a non-profit organization, works in collaboration with the Washington State Medical Association. Write for complete information. 1370 Stewart St., Seattle, Wash. 98109. Phone (206) 624-3272.

DIAGNOSTIC RADIOLOGIST—Board Certified/Eligibie, to join as third man in Department of 48 man multispecialty group. Beautiful coastal area. W. Richard Ellis, Administrator, P.O. Drawer LL, Santa Barbara, CA 93102.

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OB-GYN—The Fresno County Department of Health is looking for a person interested in Family Planning and Antenatal Clinics in rural areas. These clinics are tied into a Regional Perinatal Center and Department's Decentralization Program. Public Health interest, experience, training desirable. California license required. Spanish fluency valuable. County pays malpractice insurance and contract range is $39,000 to $43,000. Write Donald T. Rice, MD, P.O. Box 11867, Fresno, CA 93775 or call (209) 488-3953.

INTERNIST board certified or eligible, CARDIOLOGY preferred as sub-specialty, to join partnership of well established group of internists. Reply with C.V. to R. J. Bartlett, MD, 909 Hyde Street, Suite 125, San Francisco, CA 94109.

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STAFF PSYCHIATRIST—The Fresno County Department of Health has an opening in the Crisis and Out-Patient Services in a community oriented program with emphasis on multidisciplined team services. California license and Board eligibility required. Salary range from $39,955 and up depending on experience. Contact James T. Stripe, MD, Fresno County Department of Health, P.O. Box 11867, Fresno, CA or telephone (209) 488-3731.

FAMILY PRACTITIONER AND UROLOGIST for Western Colorado eleven man multispecialty group. Established practice close to skiing, hiking, trout fishing, big game hunting and year round Hot Springs swimming pools. Modern clinic facility located next to 40 bed hospital. Contact G. Thomas Morton, MD, Glenwood Medical Associates, 1905 Blake Ave., Glenwood Springs, Colorado 81601.

SHASTA COUNTY—REDDING. Shasta General Hospital vacancy for Anesthesiologist—Board certified or eligible. Modern surgical suites; fully accredited. Flexible in regard to salary and prepaid malpractice insurance or fee for service remuneration. Contact Robert Wallen, MD, 2630 Hospital Lane, Redding, CA 96001; Phone (916) 241-3232.

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UCLA SCHOOL OF MEDICINE, DEPARTMENT OF ANESTHESIOLOGY, seeks a Chairman of the Department of Anesthesiology at Kern Medical Center, its affiliate in Bakersfield, California. Board certification and California license essential. Salary open, full medical liability coverage. Interested candidates should direct inquiries or submit credentials (including curriculum vitae) to Donald F. Brayton, MD, Medical Director, Kern Medical Center, 1830 Flower Street, Bakersfield, California 93305; telephone (805) 322-3313. Both the University of California and Kern Medical Center are equal opportunity employers.

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PHYSICIANS NEEDED: Emergency Room Physicians. Excellent opportunity to practice in a delightful community in the Pacific Northwest. Modern 228-bed hospital. Excellent schools, year-round recreational activities. Write Box 9481, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 22)

(Continued from Page 21)

PHYSICIANS WANTED

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ACTIVE GP GROUP in San Joaquin Valley needs another GP as replacement for retiring doctor. Good hospital facilities, excellent living conditions and recreational facilities. Practice includes typical Class III GP work but OB and surgery open to discussion based on applicants desire. Ability to net $60,000-$70,000 second year is possible. Box No. 9480, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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CO-CHAIRMAN: ALFRED H. F. LUI, MD, Attending Staff, Department of Thoracic and Cardiovascular Surgery, White Memorial Medical Center

HONORED GUEST SPEAKER: ALTON OCHSNER, MD, Professor Emeritus of Surgery, Tulane University School of Medicine, New Orleans, Louisiana

GUEST FACULTY: JAY L. ANKENEY, MD, Professor and Director, Division of Cardiothoracic Surgery, Case Western Reserve University, Cleveland, Ohio

VIKING J. BJORK, MD, Professor and Chairman, Department of Thoracic Surgery Clinic, Karolinska Institute, Stockholm, Sweden

J. DAVID BRISTOW, MD, Professor and Chairman, Department of Medicine, University of Oregon Medical School, Portland, Oregon

J. MICHAEL CRILEY, MD, Professor of Medicine, University of California, Los Angeles, School of Medicine; Chief, Division of Cardiology, Harbor General Hospital, Torrance, California

HAROLD V. LIDDLE, MD, Assistant Clinical Professor of Thoracic and Cardiovascular Surgery, University of Utah School of Medicine, Salt Lake City, Utah

NORMAN E. SHUMWAY, MD, PhD, Professor and Chairman, Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, California

FRANK C. SPENCER, MD, Professor and Chairman, Department of Surgery, New York University School of Medicine, New York, New York

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ALCOHOLISM AND DRUG ABUSE

October 16—**Polydrug Abuse.** USC. Saturday.

CANCER

October 6—**Urological Cancer Conference—4th Annual.** Los Angeles Urological Society and American Cancer Society, California Division, at Century Plaza Hotel, Los Angeles. Monday. Contact: William Tanner, L.A. Cancer Society, 2932 Wilshire Blvd., Santa Monica 90403. (213) 828-7474.

October 9-10—**Psychosomatic Approaches to Cancer Therapy.** UC Extension and Gladman Memorial Hospital at UC, Berkeley. Saturday-Sunday. 12 hrs. Contact: Univ. of Calif. Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1064.

October 23—**Symposium on Endometrial Carcinoma.** St. John's Hospital, Santa Monica. Saturday. $30. Contact: James Moran, MD, 2200 Santa Monica Blvd., Santa Monica 90404.

October 29-30—**The Professional Team Approach to Cancer Health Care.** Claire Zellerbach Saroni Tumor Institute, Mt. Zion Hospital and Medical Center, at Hyatt Regency, San Francisco. Friday-Saturday. 11½ hrs. $110 for team (physician and one supportive professional); $85 for physician. Contact: Dept. of Continuing Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. 6 hrs. $100. Contact: CTTR, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

December 29-30—**Clinical Cancer Symposium.** USC. Wednesday-Thursday.

MEDICINE

September 15-17—**Clinical Allergy for the Office Practitioner—International Symposium.** PMC at Rickey's Hyatt House, Palo Alto. Wednesday-Friday. $25.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** Mt. Zion Hospital and Medical Center, San Francisco. Friday-Saturday. 11½ hrs. Contact: Ann Raisbeck, Dept. of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

September 18-19—**Practical Gastroenterology for the Family Physician.** UCLA. Saturday-Sunday.

September 20-May 14—**Internal Medicine Refresher Course: The State of the Art.** Medical Education Foundation of Santa Barbara County. First Monday of each month; 18 hrs. $75 for CMA members; $100, non-members. Contact: Medical Education Foundation of Santa Barbara County, 9 E. Pedregosa, Santa Barbara 93101. (805) 965-5275.

September 21—**Lyman A. Brewer, III, Cardiothoracic Symposium—2nd Annual.** White Memorial Medical Center at Hilton Hotel, Los Angeles. Tuesday. Contact: Howard Whigham, White Memorial Medical Center, 1720 Brooklyn Ave., Los Angeles 90033. (213) 269-9131, ext. 429.

September 25-October 1—**Cardiology 1976.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

September 29-30—**American Heart Association, Greater Los Angeles Affiliate—44th Annual Fall Symposium and 9th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday; 12 hrs. $60 for member of any heart assn.; $80, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 29-October 1—**San Francisco Heart Association—46th Annual Symposium.** Masonic Auditorium, San Francisco. Wednesday-Friday. Contact: S.F. Heart Assn., 259 Geary St., San Francisco 94102. (415) 982-5753.

October 1-2—**Clinical Allergy.** Children's Hospital Medical Center, Oakland, at Highlands Inn, Carmel. Friday-Saturday. Contact: Inetta Carty Calori, Med. Staff Admin. Asst., Children's Hospital Medical Center, 51st and Dover Sts., Oakland 94609. (415) 654-5600.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

October 2-3—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 8-9—**Techniques for Dermatologic Research in the Office.** UCSF. Friday-Saturday.

October 12-14—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Golden Gateway Holiday Inn, San Francisco. Tuesday-Thursday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

October 14-17—**California Society of Internal Medicine—Annual Meeting.** Del Monte Hyatt, Monterey. Thursday-Sunday. Contact: Carol Holland Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 15-16—**Internal Medicine Symposium—Neurology, Psychiatry and Internal Medicine.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-17—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 18-22—**Workshops in Internal Medicine.** American College of Physicians at University of Hawaii, Honolulu. Monday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, Pa. 19104.

October 30-November 6—**Evaluation of Neoplastic Lymphatic Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

November 3—**Echocardiography.** LLU. Wednesday. 6 hrs.

November 3—**Respiratory Diseases.** Donald N. Sharp Memorial Community Hospital, San Diego. Wednesday. $10 for members of Sharp; $20, non-members. Contact: Milo A. Youel, MD, Dir., CME, Donald N. Sharp Memorial Community Hosp., 7901 Frost St., San Diego 92123. (714) 292-2121.

November 6-7—**Dermatologic Surgery—Skin Grafting.** See Surgery, November 6-7.

November 8-12—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 10—**Hypertension.** UCSF at Hyatt on Union Square, San Francisco. Wednesday.

November 13-14—**Kidney Function.** UCSF. Saturday-Sunday.

November 27-29—**Advances in Heart Disease—1977.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

December 8-10—**Respiratory Failure Workshop.** USC at Canyon Hotel, Palm Springs. Wednesday-Friday.

December 11—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. $250.

MENTAL RETARDATION

November 3-5—**Current Aspects of Mental Retardation.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

OBSTETRICS AND GYNECOLOGY

September 15-22—**Workshops in (1) High Risk Pregnancy and (2) Infertility.** UCSF at Royal Lahaina Hotel, Maui, Hawaii. One week.

October 1-3—**Symposium on Perinatal Medicine.** National Foundation/March of Dimes; Long Beach and Orange County Obstetrics-Gynecology Societies; UCI at Memorial Hospital Medical Center, Long Beach. Friday-Sunday. $150. Contact: Executive Secretary, Center for Health Education, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3823.

October 2—**Endometriosis: Current Principles and Management—16th Annual Fall Seminar in Obstetrics and Gynecology.** Shufelt Society of Santa Clara Valley at Le Baron Hotel, San Jose. Saturday. 7 hrs. Contact: Vincent F. Nola, MD, Sect., Shufelt Society, 2081 Forest Ave., San Jose 95128.

October 5-8—**Fetal Monitoring.** USC. Tuesday-Friday.

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October 6-8—**Recent Trends in Ob-Gyn.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

October 8-9—**Office Gynecology.** PMC at Hyatt on Union Square, San Francisco. Friday-Saturday. $90.

October 23—**Symposium on Endometrial Carcinoma.** See Cancer, October 23.

October 25-26—**New Horizons in Perinatal Intensive Care—5th Annual Seminar.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. Contact: Robin J. Grant, MPH, Coord. of Cont. Ed., Harbor General Hospital, 1124 W. Carson, Torrance 90502. (213) 328-2380, ext. 1374.

October 25-29—**Ob/Gyn Review.** USC at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

October 29—**Advances in Obstetrics and Gynecology.** UCD and Northern California Ob-Gyn Society at Red Lion Motor Inn, Sacramento. Friday. Contact: UCD.

PEDIATRICS

September 22-23—**Brennemann Memorial Lectures—33rd Annual.** Los Angeles Pediatric Society at Sportmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Gene Black, LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 22-23—**Nutrition in Children.** UCD and Sacramento Pediatric Society at Red Lion Motor Inn, Sacramento. Friday-Saturday. $45.

November 8-12—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 8-12.

December 4—**American Academy of Pediatrics, California Chapter I, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

PSYCHIATRY

September 15—**Office Psychiatry.** LLU. Wednesday. 6 hrs.

October 9—**Psychological Management of Chronic Pain.** UCLA. Saturday. 6½ hrs. $95.

November 8-12—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

December 2-5—**Treatment of Sexual Dysfunctions.** See Of Interest To All, December 2-5.

RADIOLOGY AND PATHOLOGY

September 18—**Radiology Symposium.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 1-3—**Society of Nuclear Medicine—1st Annual Western Regional Meeting.** Fairmont Hotel, San Francisco. Friday-Sunday. Contact: Justine J. Lynch, Exec. Sec., No. and So. Calif. and Pacific NW Chapters, SNM, P.O. Box 40279, San Francisco 94140.

October 2—**Speech Pathology. USC.** Saturday.

October 15-17—**Radiology of the Genitourinary System.** American College of Radiology at Fairmont Hotel, San Francisco. Friday-Sunday. 15 hrs. $200 for members; $240, nonmembers. Contact: Maurine H. Trautz, Conf. Coord., ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015. (301) 654-6900.

October 21-29—**American Society of Clinical Pathologists and College of American Pathologists.** Hilton Hotel, Los Angeles. Nine days. Contact: D. L. Gilcrest, ASCP, 2100 W. Harrison St., Chicago 60612.

October 26-29—**Symposium in Diagnostic Radiology.** UCSD at Vacation Village, San Diego. Tuesday-Friday.

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** See Cancer, December 12.

SURGERY AND ANESTHESIOLOGY

September 15-16—**Strabismus.** PMC at Stanford Court Hotel, San Francisco. Wednesday-Thursday. $175.

September 16-17—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 9-13—**American Society of Anesthesiologists—Annual Meeting.** Hilton Hotel, San Francisco. Saturday-Wednesday. 45 hrs. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

October 10-22—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. 100 hrs. $1200 for otolaryngologists; $900, residents. Contact: Jack L. Pulec, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

October 11-12—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Monday-Tuesday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

October 14-15—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

October 15-17—**Regional Anesthesia.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Monterey. Friday-Sunday. 9½ hrs. Contact: Stuart F. Sullivan, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

October 26-November 30—**Surgical Anatomy and Surgery.** USC. Tuesday evenings.

November 5-6—**Clinical Electromyography.** American Association of Electromyography and Electrodiagnosis at Sheraton-Harbor Island, San Diego. Friday-Saturday. 12 hrs. $100. Contact: W. C. Wiederholt, MD, 7010 Via Valverde, La Jolla 92037. (714) 459-8443.

November 6—**Bilateral Cleft Lip and Palate—Problems of Diagnosis and Treatment—8th Annual Symposium.** St. John's Hospital and Health Center, Santa Monica. Saturday. Contact: Cleft Palate Service, St. John's Hosp. and Health Ctr., 1328 22nd St., Santa Monica 90404. (213) 829-5511, ext. 2745.

November 6-7—**Dermatologic Surgery—Skin Grafting.** UCSF. Saturday-Sunday.

November 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 13—**Flexible Bronchofibroscopy Workshop.** PMC. Saturday. $250.

November 13—**Ophthalmological Emergencies for Emergency Department Physicians and Nurses.** Memorial Hospital Medical Center of Long Beach. Saturday. $50. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

November 27-28—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Saturday-Sunday. $300; $150 for residents.

December 2-3—**Medical and Surgical Complications of Uveitis.** UCSF. Thursday-Friday.

December 3-4—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hosp. Med. Ctr., 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

December 3-5—**Electronystagmography Workshop.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

December 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

December 11—**Anesthesia Update: New Agents and Techniques.** Valley Anesthesia Society of Sacramento, UCD and Calif. Society of Anesthesiologists at Red Lion Inn, Sacramento Saturday. Contact: John H. Eisele, MD, Dept. of Anesthesiology, UCD School of Medicine, Davis 95616.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

September 15—**Office Psychiatry.** See Psychiatry, September 15.

September 17-18—**Neurology for the Non-Neurologist: Common Problems of Neurology for the Internist and Family Practitioner.** See Medicine, September 17-18.

September 18-19—**Practical Gastroenterology for the Family Physician.** See Medicine, September 18-19.

September 20-24—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

September 20-24—**Topics in Emergency Medicine—Basic Course.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

September 28-December 12—**Bedside Clinics.** USC. Tuesdays.

October 7-9—**Western Occupational Health Conference—20th Annual.** Western Occupational Medical Association at Marriott Hotel, Los Angeles. Thursday-Saturday. Contact: Jack Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 9—**Psychological Management of Chronic Pain.** See Psychiatry, October 9.

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For further information contact the Office of Conferences and Institutes (702) 739-3394.

October 11-15—**Primary Care.** STAN. Monday-Friday. $250.

October 21-22—**Old Age—Program on Geriatrics.** UCSF at Veteran's Home of California, Napa. Thursday-Friday.

October 24-27—**California Academy of Family Physicians.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: William R. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

October 25-29—**Family Practice Review.** LLU. Monday-Friday.

October 25-29—**Global Medicine and Diseases of Travel—120th Annual Scientific Meeting.** Hawaii Medical Association at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., HMA, 510 S. Beretania St., Room 201, Honolulu 96813. (808) 536-7702.

October 30-31—**Physiology of Respiration.** UCSF. Saturday-Sunday.

November 1-5—**Intensive Care.** STAN. Monday-Friday. $250.

November 1-5—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday.

November 5-6—**Clinical Electromyography.** See Surgery, November 5-6.

November 6—**Bilateral Cleft Lip and Palate—Problems of Diagnosis and Treatment.** See Surgery, November 6.

November 7-12—**American Academy of Physical Medicine and Rehabilitation.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: C. C. Herold, Exec. Dir., AAPMR, 30 N. Michigan Ave., Suite 900, Chicago, Ill. 60602.

November 11-12—**Emergency Medicine (Advanced Course).** UCSF. Thursday-Friday.

November 11-12—**New Concepts in Medicine.** California Hospital Medical Center, Los Angeles. Thursday-Friday. 11 hrs. $25. Contact: K. L. Senter, MD, Dir., Med. Ed., Calif. Hosp. Med. Ctr., 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

November 12-14—**Primary Care—2nd Annual Postgraduate Seminar.** Stanford; Mission Bay Hospital, San Diego; Hyatt Medical Management Services, Encino, at Del Monte Hyatt House, Monterey. Friday-Sunday. Contact: Jay Beeler, Dir. of Public Relations, Hyatt Medical Management Services, 16633 Ventura Blvd., Suite 1325, Encino 91436. (213) 990-2000.

November 13—**Ophthalmological Emergencies for Emergency Department Physicians and Nurses.** See Surgery, November 13.

November 15-19—**Dermatology for Primary Care Physicians.** UCSF. Monday-Friday. $400. Intensive preceptorial course presenting practical management of skin diseases that constitute a large part of daily practice. Enrollment limited to 10 primary care providers.

November 19—**Diuretics.** USC. Friday.

December 1-3—**Immunizations—Review and Predictions.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

December 2-5—**Treatment of Sexual Dysfunctions.** USC at Canyon Hotel, Palm Springs. Thursday-Sunday.

December 9-11—**Genetics.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday.

December 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

FAMILY PRACTICE

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith. MD, Department of Family Practice, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

September 18-19—**Advanced Life Support—Emergency Cardiac Care.** Providence Hospital, Portland. Contact: C. A. Hites, MD, 1500 S.W. 12th Avenue, Portland 97201.

September 22-24—**Oregon Medical Association Annual Scientific Session.** Hilton Hotel, Portland. Contact: Sondra Gleason, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

October 1—**Oregon Gut Club Symposium.** University of Oregon Health Sciences Center, University Hospital South, 8B60, Portland. Contact: Clifford Melnyk, MD, Department of Gastroenterology, University of Oregon Health Sciences Center School of Medicine, 3181 S.W. Sam Jackson Park Road, Portland 97201.

October 21-22—**Annual Postgraduate Course in Surgery and Medicine.** Providence Hospital, Portland. Contact: Joseph E. Gambee, MD, Department of Family Practice, Providence Hospital, 700 N.E. 47th Avenue, Portland 97213.

WASHINGTON, MONTANA, ALASKA and IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

September 23-24—**Ophthalmology and Otolaryngology for Primary Physicians.** Thursday-Friday. Registration: T-639 Health Sciences Building, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 1-2—**Annual Cancer Conference.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. No fee. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 6—**Internal Medicine Review Sessions.** Wednesday evenings to June 1. T-625 Health Sciences Building, Univ. of Wash. Sch. of Med., Seattle. Hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 6-8—**Clinical Topics in Chest Disease.** (ACP). Wednesday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 19½ hrs. Fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 7-8—**Hospital and Health Facilities Infectious Disease Control.** Thursday-Friday. Health Sciences Building Auditorium, Univ. of Wash., Seattle. Hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 7-9—**Montana Medical Association Annual Meeting.** Thursday-Saturday. Heritage Inn, Great Falls, MT. Contact G. B. Zins, Exec. Dir., 2021 11th Ave., Helena, MT 59601.

October 7-9—**West Coast Allergy Society Annual Scientific Program.** Thursday-Saturday. Washington Plaza Hotel, Seattle. Contact: William H. Wilson, MD, Program Chairman, West Coast Allergy Society, 2164 S.W. Park Place, Portland, OR 97205. (503) 226-1555.

October 9-12—**Mountain Medicine Symposium.** Sunday-Tuesday. Providence Heights Conference Center, Issaquah. $47. Contact: Providence Heights Conference Center, 4221 228th SE, Issaquah, WA 98027.

October 11-15—**University of Washington School of Medicine Eastern Washington Circuit Course on Pain.** 11, Moscow, ID; 12, Walla Walla; 13, Tri-Cities; 14, Yakima; 15, Wenatchee. Hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 15-17—**Western Dialysis and Transplant Society Annual Meeting.** Friday-Sunday. Olympic Hotel, Seattle. Physicians, $30; others, $20. Contact: Linda J. Huprich, Convention Mgr., 11633 Ventura Blvd., Encino, CA. (213) 981-0554.

October 22-23—**Aging and the Elderly.** Friday-Saturday. Seattle. Location, hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 22-23—**Sports Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 25-29—**The Endocrine Society's Twenty-Eighth Annual Postgraduate Assembly.** Monday-Friday. Olympic Hotel, Seattle. 31½ hrs. $185. Contact: Mrs. Nettie C. Karpin, Exec. Secty., The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20014.

November 1—**Internal Medicine Review: Dermatology.** Monday. Univ. of Wash. in Wenatchee. Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

November 2—**Internal Medicine Review: Dermatology:** Tuesday. Univ. of Wash. in Yakima. Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

November 4-5—**Current Concepts in Drug Therapy.** Thursday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 11-12—**Arthritis.** Thursday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 12—**Newer Approaches to the Same Old Headaches.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

November 17—**Allergy.** Wednesday. Univ. of Wash. in Anacortes, Wash. Island Hospital, 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 293-3101.

November 18—**Internal Medicine Review: Medical Genetics.** Thursday. Univ. of Wash. in Billings, Mont. Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

November 19—**Internal Medicine Review: Medical Genetics.** Friday. Univ. of Wash. in Missoula, Mont. St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59101. (406) 549-4581.

November 19—**Treating the Untreatable.** Friday. Spokane. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 22—**Internal Medicine Review: Nuclear Medicine.** Monday. Univ. of Wash. in Wenatchee. Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

November 23—**Internal Medicine Review: Nuclear Medicine.** Tuesday. Univ. of Wash. in Yakima. Wash. Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima WA 98902. (509) 663-8711.

November 30—**Surgery: Shock and Clinical Fluid Balance.** Tuesday. Univ. of Wash. in Missoula, Mont. 2 hrs. Contact: Leonard W. Brewer, MD, 2833 Ft. Missoula Rd., Missoula, MT 59801. (406) 728-6815.

December 1—**Surgery: Shock and Clinical Fluid Balance.** Wednesday. Univ. of Wash. in Billings, Mont. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

December 3-4—**Medical Genetics.** Friday-Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

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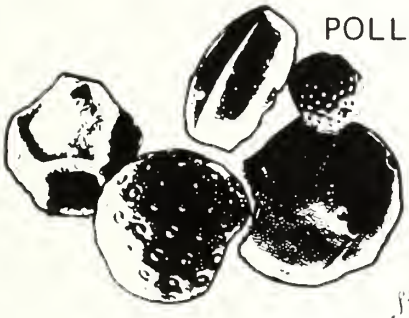

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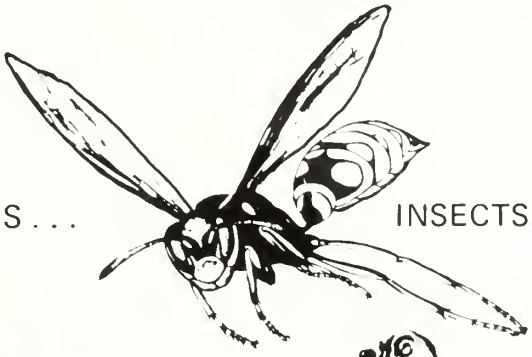

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REFERENCES

M. Ceska, R. Eriksson, and J.M. Varga
Radioimunosorbent Assay of Allergens —
The Journal of Allergy and Clinical Immunology
Vol. 49, No. 1-9, 1972

Wide L. et. al
Diagnosis of Allergy by an In Vitro Test for Allergen Antibodies
Lancet 2:1105, 1967

A. F. Lopapa, W.R. MacLaren
An In Vitro Test as used in the detection of immediate hypersensitivity in man.
V Latin American Congress of Allergy and Immunology National Academy of Medicine
Buenos Aires, Argentina, October 1974

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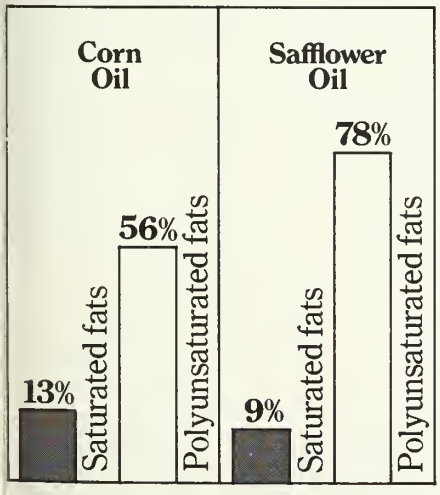

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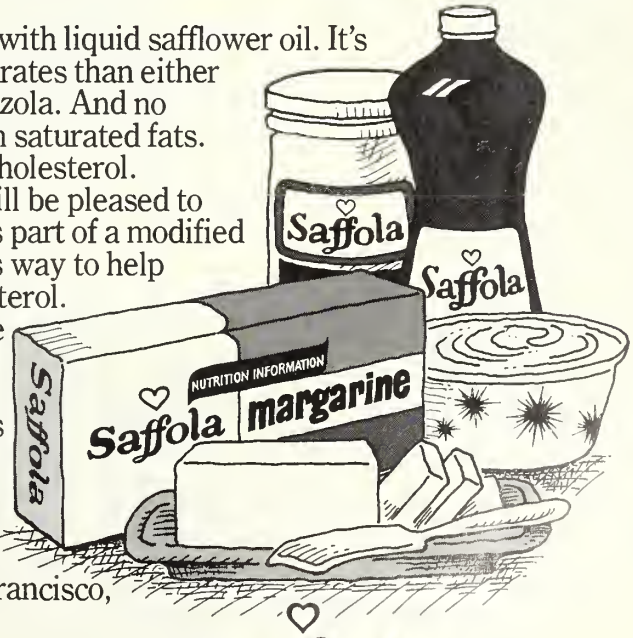

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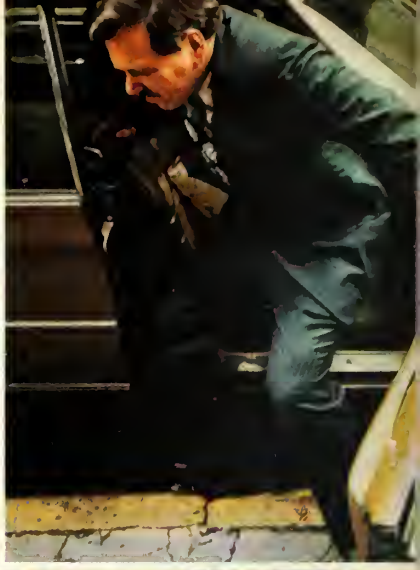

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1. Hindle, T.H. III: Calif. Med. *117:7* (Aug.) 1972. 2,3. Unpublished Data on file, Medical Department, Wallace Laboratories, Cranbury, N.J.

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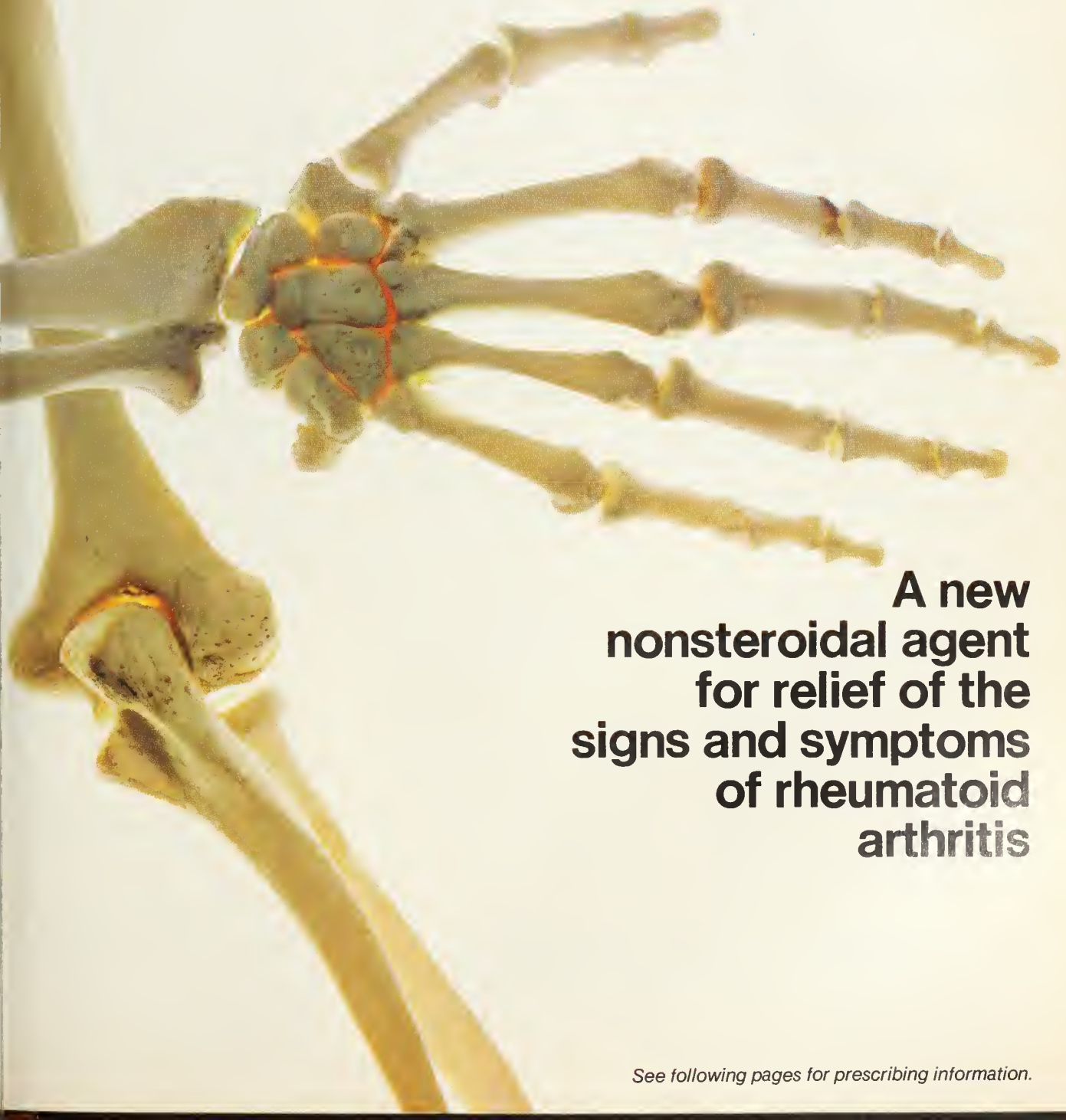
New from
Lilly/Dista Research

NALFON®
fenoprofen calcium



A new
nonsteroidal agent
for relief of the
signs and symptoms
of rheumatoid
arthritis

See following pages for prescribing information.

NALFON®
fenoprofen calcium

...reduces the pain and inflammation of rheumatoid arthritis* ...and it is well tolerated

New propionic acid derivative

NALFON® (fenoprofen calcium)
300-mg.† Pulvules®

- Relieves arthritic pain
- Reduces inflammation
- Improves function and mobility
- Well tolerated
- Chemically unrelated to aspirin, indomethacin, phenylbutazone, or corticosteroids

600472

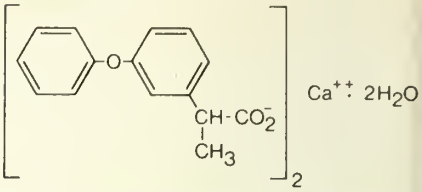
DISTA

*The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care).

†Present as 345.9 mg. of the calcium salt of fenoprofen dihydrate equivalent to 300 mg. fenoprofen

Description: Pulvules® Nalfon® (fenoprofen calcium, Dista) for oral administration contain fenoprofen calcium as the dihydrate in an amount equivalent to 300 mg. of fenoprofen. Nalfon is a nonsteroidal, anti-inflammatory drug. Chemically it is a propionic acid derivative.

The structural formula is as follows:



Calcium dl-2-(3-phenoxyphenyl) propionate dihydrate.

Nalfon is a white crystalline powder, soluble in U.S.P. ethanol (95%) to the extent of approximately 15 mg./ml. at 25 C°; slightly soluble in water, and insoluble in benzene.

The pKa of Nalfon is 4.5 at 25° C.

Clinical Pharmacology: Nalfon is a nonsteroidal, anti-inflammatory, anti-arthritic compound. In animal systems, it also shows analgesic and antipyretic activity. Its mode of action is unknown. In patients with rheumatoid arthritis, the anti-inflammatory action of Nalfon has been shown by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion. Its action is not mediated through the adrenal gland. There is no evidence that Nalfon alters the progressive course of the underlying disease.

To further demonstrate the anti-inflammatory activity of Nalfon in humans, the emergence and degree of erythemic response were measured in adult male volunteers exposed to ultraviolet irradiation. The effects of Nalfon, aspirin, and indomethacin were compared separately with those of placebo. All three drugs demonstrated anti-erythemic activity. The results in humans confirmed the anti-inflammatory activity found in animals.

Nalfon has been shown to inhibit prostaglandin synthetase isolated from bovine seminal vesicles. Reproduction studies in rats have shown Nalfon to be associated with prolonged labor and difficult parturition when given during late pregnancy. Evidence suggested that this may be due to decreased uterine contractility resulting from the inhibition of prostaglandin synthesis.

Under fasting conditions, Nalfon is rapidly absorbed, achieving peak plasma levels of 50 mcg. per ml. within two hours of oral administration of 600 mg. doses. Good dose proportionality was observed between 200 mg. and 600 mg. in fasting male volunteers. The plasma half-life is approximately 3 hours. Approximately 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4′-hydroxyfenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin.

The coadministration of aspirin decreases the biologic half-life of fenoprofen due to an increase in metabolic clearance which results in a greater amount of hydroxylated fenoprofen in the urine. Although the mechanism of interaction between fenoprofen and aspirin is not totally known, enzyme induction or displacement of fenoprofen from plasma albumin binding sites are possibilities. Chronic administration of phenobarbital, a known enzyme inducer, may be associated with a decrease in plasma half-life of fenoprofen. Clinical significance of these interactions is not known.

The concomitant administration of antacid (aluminum and magnesium hydroxide) does not interfere with absorption of Nalfon. Food ingestion decreases the rate and extent of absorption of Nalfon.

With single doses of Nalfon there is less suppression of collagen-induced platelet aggregation than with aspirin.

Fenoprofen shows anti-inflammatory effects in rodents by inhibiting the development of redness

and edema in acute inflammatory conditions and by reducing soft-tissue swelling and bone damage associated with chronic inflammation. It exhibits analgesic activity in rodents by inhibiting the writhing response in mice caused by the introduction of an irritant into the peritoneal cavity and by elevating pain thresholds to pressure in edematous hindpaws of rats. In rats made febrile by the subcutaneous administration of brewer's yeast, fenoprofen produces antipyretic action. These effects are characteristic of nonsteroidal, anti-inflammatory, antipyretic, analgesic drugs.

Indications and Usage: Nalfon® (fenoprofen calcium, Dista) is indicated for relief of the signs and symptoms of rheumatoid arthritis. It is indicated in the treatment of acute flares and in the long-term management of the disease. The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV. (Incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care.) Improvement in patients treated with Nalfon for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in the duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and the patient, and by increased mobility as demonstrated by a reduction in the number of joints with limited motion.

In clinical studies in patients with rheumatoid arthritis, Nalfon has been shown to be comparable to aspirin in controlling the aforementioned measures of disease activity but the frequency of the milder gastrointestinal adverse effects (nausea, dyspepsia) and tinnitus was less than in aspirin-treated patients. It is not known whether Nalfon causes less peptic ulceration than aspirin.

In some patients Nalfon has been used in combination with gold salts or corticosteroids. Studies have been inadequate to demonstrate whether Nalfon adds any improvement in patients maintained on gold salts or corticosteroids. Whether Nalfon could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. The use of Nalfon in combination with salicylates is not recommended because there is no evidence to demonstrate that Nalfon would produce any additional effect beyond that produced by aspirin alone. Further, there is evidence that aspirin increases the rate of excretion of Nalfon.

There have been no studies in children; therefore the safety and effectiveness of Nalfon in children are unknown.

Contraindications: Nalfon is contraindicated in patients who have shown hypersensitivity to it.

Because the potential exists for cross sensitivity to aspirin and other nonsteroidal, anti-inflammatory drugs, Nalfon should not be given to patients in whom aspirin and other nonsteroidal, anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria.

Warnings: Nalfon should be given under close supervision to patients with a history of upper gastro-intestinal tract disease and only after consulting the "ADVERSE REACTIONS" section. Gastro-intestinal bleeding, sometimes severe, has been reported in patients receiving Nalfon.

In patients with active peptic ulcer and active rheumatoid arthritis, attempts should be made to treat the arthritis with nonulcerogenic drugs, such as gold. If Nalfon must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding.

In subacute and chronic studies in rats, Nalfon caused interstitial nephritis, glomerulonephritis and renal papillary necrosis. These abnormalities were dose-related and began to appear at doses approximating the human dose. In chronic studies in monkeys interstitial nephritis also occurred following Nalfon administration. Although this was seen at doses considerably above the human dose, lower doses were not studied in this species. During the course of the clinical trials one patient developed renal failure and died with a diagnosis of septicemia, bilateral suppurative pyelonephritis and renal papillary necrosis. It is not known whether these events were drug-related. A few patients developed mild elevations of the BUN during Nalfon® (fenoprofen calcium, Dista) therapy. Since Nalfon is eliminated primarily by the kidney, the drug should not be administered to patients with significantly impaired renal function. It is desirable to perform periodic renal function tests in all patients receiving Nalfon.

Precautions: In chronic studies in rats, high doses of Nalfon caused elevation of serum transaminase and hepatocellular hypertrophy. In clinical trials, some patients developed elevation of serum transaminase, LDH, and alkaline phosphatase which persisted for some months, and usually, but not always, declined despite continuation of the drug. The significance of this is unknown. It is recommended that periodic liver function tests be performed in patients receiving Nalfon and that the drug be discontinued if abnormalities occur.

The safety of this drug in pregnancy and lactation has not been established and its use during these events is, therefore, not recommended. Reproduction studies have been performed in rats and rabbits. When fenoprofen was given to rats during pregnancy and continued to the time of labor, parturition was prolonged. Similar results have been found with other nonsteroidal, anti-inflammatory drugs which inhibit prostaglandin synthetase.

In-vitro studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs which are also albumin bound and may lead to drug interaction. Theoretically, fenoprofen, as well as other nonsteroidal, anti-inflammatory agents, could likewise be displaced. Patients receiving hydantoin, sulfonamides, or sulfonylureas should be observed for signs of toxicity to these drugs. In patients receiving coumarin-type anticoagulants, the addition of Nalfon to therapy could prolong the prothrombin time. Patients receiving both drugs should be under careful observation.

In patients receiving concomitant Nalfon-steroid therapy, any reduction of steroid dose should be gradual to avoid the possible complications of sudden steroid withdrawal.

Patients with initial low hemoglobin values who are receiving long term Nalfon therapy should have a hemoglobin determination at reasonable intervals.

Peripheral edema has been observed in some patients taking Nalfon; therefore, Nalfon should be used with caution in patients with compromised cardiac function.

Studies to date have not shown changes in the eye attributed to Nalfon administration. However, because of adverse eye findings in animal studies with some other nonsteroidal anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after starting chronic Nalfon therapy and at periodic intervals thereafter.

Since food decreases Nalfon blood levels, the drug should be given 30 minutes before or two hours after meals during the daytime.

When phenobarbital, which may enhance the metabolism of Nalfon, is added or withdrawn, Nalfon dosage adjustment may be required.

Caution should be exercised by patients whose activities require alertness if they experience central nervous system side effects from Nalfon.

Since the safety of Nalfon in patients with impaired hearing loss has not been established, these patients should have periodic tests of auditory function when chronic Nalfon therapy is given.

Nalfon decreases platelet aggregation and prolongs bleeding time. Patients who may be adversely affected by prolongation of the bleeding time should be carefully observed when Nalfon is administered.

Adverse Reactions: *Digestive System*

The most common type of adverse reaction concerned the gastro-intestinal system. Dyspepsia occurred most frequently, being observed in about one out of seven patients. Other adverse reactions in descending order of frequency were: constipation, nausea, vomiting, abdominal pain, anorexia, occult blood in the stool, diarrhea, flatulence, and dry mouth.

Three instances of peptic ulceration and/or gastro-intestinal hemorrhage that may have been due to the drug and four instances in which drug relationship was questionable were observed in 3,391 individuals to whom the drug was administered for periods of time ranging up to 165 weeks.

In less than 2% of patients the drug was discontinued because of adverse gastro-intestinal reactions.

Skin and Appendages

The most common adverse effect was pruritus which was seen in about one out of ten patients. Other adverse reactions were: rash, increased sweating, and urticaria.

In about 1% of patients Nalfon® (fenoprofen calcium, Dista) was discontinued due to an adverse effect related to the skin.

Nervous System

The most frequent adverse reaction observed was somnolence which occurred in about one out of seven patients. Other adverse effects which occurred less frequently were: dizziness, tremor, confusion, and insomnia.

Nalfon was discontinued in less than 0.2% of patients because of these side effects.

Special Senses

The most common adverse reaction was tinnitus which was seen in about one out of ten patients. Other reactions observed in descending order of frequency were: blurred vision and decreased hearing.

In about 0.2% of patients Nalfon was discontinued due to adverse effects related to the special senses.

Cardiovascular

The most frequent adverse event observed was palpitations. This was noted in about one out of 25 patients. Tachycardia was observed less frequently.

In less than 0.5% of patients Nalfon was discontinued due to cardiovascular adverse reactions.

Laboratory

Anemia was noted in about one out of 500 patients. One patient required discontinuation of Nalfon therapy due to anemia. Increase in alkaline phosphatase, LDH, and SGOT were observed. ("See Precautions.")

Miscellaneous

Headache was seen in about one out of seven patients. Less frequently observed in descending order of frequency were: nervousness, asthenia, dyspnea, peripheral edema, fatigue, malaise, dysuria.

Overdosage: No specific information is available on the treatment of overdosage with Nalfon. If it should occur, standard procedures to evacuate gastric contents and to support vital functions should be employed. Since Nalfon is acidic and is excreted in the urine, it may be beneficial to administer alkali and induce diuresis. Furosemide (Lasix®) did not lower blood levels.

Dosage and Administration: For the initial treatment of rheumatoid arthritis, the recommended oral dose is 600 mg. four times a day. Although improvement may be seen in a few days in many patients, an additional two to three weeks may be required to gauge the full benefits of therapy. The dosage should be adjusted in accordance with the patient's condition and changes in disease activity. Daily dosage larger than 3200 mg. is not recommended. Nalfon should be administered 30 minutes before or at least two hours after meals. If gastro-intestinal complaints occur, administer Nalfon with meals or milk.

There have been no studies in children; therefore, the safety and effectiveness of Nalfon in children are unknown.

How Supplied: Pulvules Nalfon, 300 mg. (equivalent to fenoprofen), are supplied in bottles of 60 and 500 (No. 416). They are yellow and ocher in color. The Identi-Code® (formula identification code, Dista) symbol is H77.

DISTA 600472

Additional information available to the profession on request.

DISTA PRODUCTS COMPANY
Division of Eli Lilly and Company
Indianapolis, Indiana 46206

contains no aspirin

tablets

Darvocet-N® 100

100 mg. Darvon-N® (propoxyphene napsylate)
650 mg. acetaminophen

recommended dosage:
one tablet q. 4 h.
p. r. n. for pain

See summary of prescribing information on adjoining page.

a potent analgesic for relief of mild to moderate pain

DARVOCET-N® 100
propoxyphene napsylate with acetaminophen

Indications: For the relief of mild to moderate pain, either alone or accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants, including alcohol.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions. [011375A]

Additional information available to the profession on request.

600702

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Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

MAKES SENSE FOR LONG-TERM CONTROL OF HYPERTENSION*

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **WARNING**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the fixed combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium-sparing action of its 'Dyrenium' component is warranted.

Contraindications: Further use in progressive renal or hepatic dysfunction; hyperkalemia. Preexisting elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs. Routine use of diuretics in otherwise healthy pregnancy.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in severely ill patients with urine volume less than one liter/day, the elderly or diabetics, with suspected or confirmed renal insufficiency. Periodic determinations of serum K^+ should be made. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **The presence of a widened QRS complex or arrhythmia in association with hyperkalemia requires prompt additional therapy.** Thiazides are reported to cross the placental barrier and appear in breast milk; fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions that have occurred in the adult may result. When used in pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics, or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium® (triamterene, SK&F Co.), and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Do periodic blood studies in cirrhotics to check for nondrug-related variations in blood pictures, and in patients with folic acid depletion, since 'Dyrenium' may contribute to appearance of megaloblastosis. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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The foods above have several nutrients in common. Among them are the vitamin B complex, necessary for healthy skin and a well-functioning nervous system. The B vitamins include thiamin (B_1), niacin and riboflavin (B_2). These foods are classified as the Bread & Cereal Group in the U.S. Department of Agriculture's Four Food Groups system.

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Dairy Council of California

The Four Food Groups—milk, meat, vegetables and fruits, breads and cereals—a practical guide to good nutrition.

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Antivert®/25
(meclizine HCl) 25 mg. Tablets
for vertigo*

▪ **Most Widely Prescribed**—Antivert is the most widely prescribed agent for the management of vertigo* associated with diseases affecting the vestibular system such as Menière's disease, labyrinthitis, and vestibular neuronitis.

▪ **Relief of Nausea and Vomiting**—Antivert/25 can relieve the nausea and vomiting often associated with vertigo.*

▪ **Dosage for Vertigo***—The usual adult dosage for Antivert/25 is one tablet t.i.d.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE LUNG IN THE CRITICALLY ILL PATIENT—Pathophysiology and Therapy of Acute Respiratory Failure—Select articles from "Critical Care Medicine": Edited by William C. Shoemaker, MD, Professor of Surgery, UCLA, Harbor General Hospital, Torrance, California. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1976. 128 pages, $9.50.

MEDICAL MICROBIOLOGY—Twelth Edition: Volume II—The Practice of Medical Microbiology—Robert Cruickshank, CBE, MD, FRCP, FRCPE, DPH, FRSE, Hon LL D(Aberd), Professor Emeritus of Bacteriology, University of Edinburgh; J. P. Duguid, MD, BSc, FRC Path, Professor of Bacteriology, University of Dundee; Consultant in Bacteriology, Tayside Health Board; Consultant Advisor in Microbiology, Scottish Home and Health Department; B. P. Marmion, MD, DSc, FRC Path, FRCPE, FRSE, Professor of Bacteriology, University of Edinburgh; Chief Bacteriologist, Royal Infirmary, Edinburgh; and R. H. A. Swain, MA, MD, FRCPE, FRC Path, FRSE, Reader in Virology, University of Edinburgh; Consultant in Virology, Royal Infirmary, Edinburgh. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 588 pages, $22.00.

MENTAL HEALTH AND DISEASE IN AFRICA: With Special Reference to Africa South of the Sahara—Charles R. Swift, MD, Professor of Psychiatry, Faculty of Medicine, University of Dar es Salaam, Dar es Salaam, Tanzania; and Tolani Asuni, MD, DPM, FRC Psych, FNMC Psych, Medical Superintendent, Neuro-Psychiatric Hospital, Aro, Abeokuta, Nigeria. Churchill Livingston Medical Division, Longman, Inc., 19 West 44th St., New York Cty (10036), 1975. 257 pages, $9.50.

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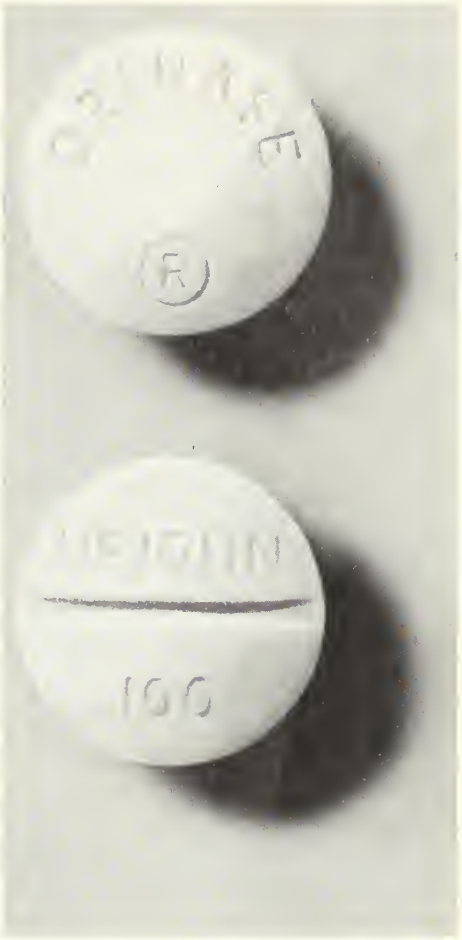

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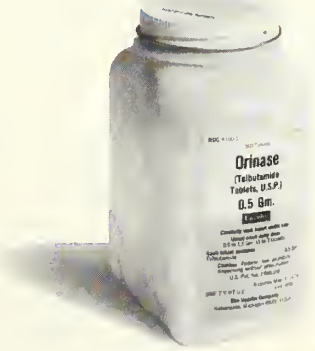

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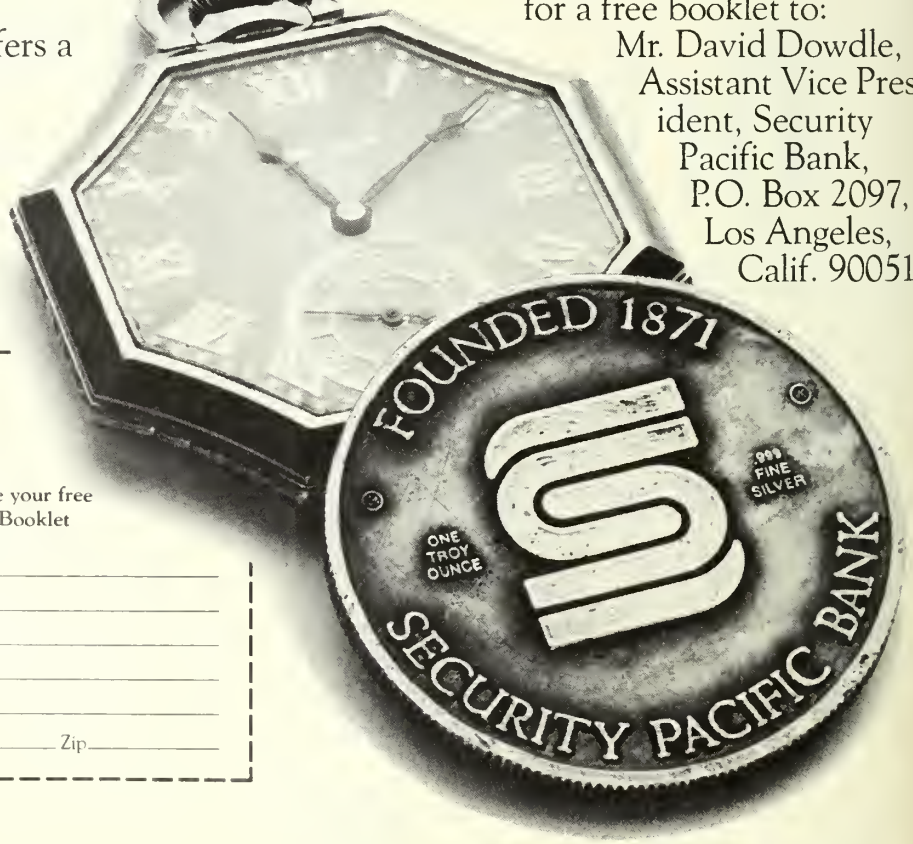

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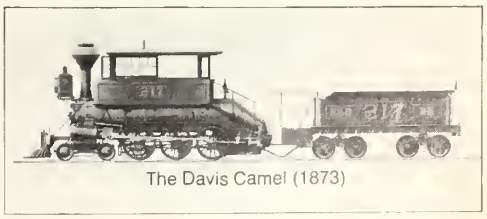

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Intraaortic Balloon Pumping Assist Following Open Heart Surgery for Coronary Artery Disease

SUSUMU NAKANO, MD; JEROME HAROLD KAY, MD; PABLO ZUBIATE, MD; A. MICHAEL MENDEZ, MD, *and* NEAL VANSTROM, MD, *Los Angeles*

Intraaortic balloon pump (IABP) assist was employed in 36 patients after surgical operation for coronary artery disease. In 31 patients, the aid of IABP was required because cardiopulmonary bypass could not be terminated without it. In three of these patients, IABP assist was started before the surgical procedure because these patients were in cardiogenic shock due to myocardial infarction. In the remaining five patients, IABP assist was applied for refractory cardiogenic shock in the early postoperative period.

The overall survival rate was 58 percent. IABP assist was used in 13 patients with an ejection fraction of 0.1 to 0.2 (normal 0.7). Nine of these patients survived.

From our experience, it would appear that this temporary mechanical circulatory support provides a significant advantage in saving patients who might otherwise die after surgical procedures involving the coronary artery.

INTRAAORTIC BALLOON PUMP (IABP) assist has been employed for the treatment of cardiogenic shock secondary to acute myocardial infarction.[1] It augments myocardial perfusion and decreases the left ventricular afterload. This device has also been used for the treatment of intraoperative myocardial failure following cardiopulmonary bypass.

The purpose of this study is to review our clinical experience with 36 patients supported with IABP assist following surgical procedures on the coronary artery.

From the Los Angeles Heart Institute at the St. Vincent Medical Center and the University of Southern California School of Medicine, Los Angeles.

Submitted, revised, January 6, 1976.

Aided by grants from the Children's Heart Foundation and the Los Angeles Thoracic and Cardiovascular Foundation.

Reprint requests to: Jerome Harold Kay, MD, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033.

Material and Method

From May 1972 to March 1975, myocardial revascularization was carried out in 1,479 patients. The intraaortic balloon pump was used for 36 of these patients before or following coronary artery surgical procedures. These patients were divided into two groups.

Group I consisted of 31 patients in whom IABP assistance was used following surgical operation because of inadequate circulation on termination of cardiopulmonary bypass. IABP assist was initiated before operation in three of these patients who were in cardiogenic shock due to acute myocardial infarction.

Group II consisted of the remaining five patients in whom IABP assist was required for refractory cardiogenic shock in the early post-

TABLE 1.—*Preoperative Status of 36 Patients*

	Patients	*Deaths*
Coronary artery disease with or without poor ejection fraction	19	8
Complications secondary to acute myocardial infarction	7	1
Unstable anginal syndrome	7	4
Acute myocardial infarction with cardiogenic shock	3	2
TOTAL	36	15
Left Ventricular Impairment		
Ejection Fraction		
0.2 or less	13	4
0.25 to 0.7	23	11
TOTAL	36	15

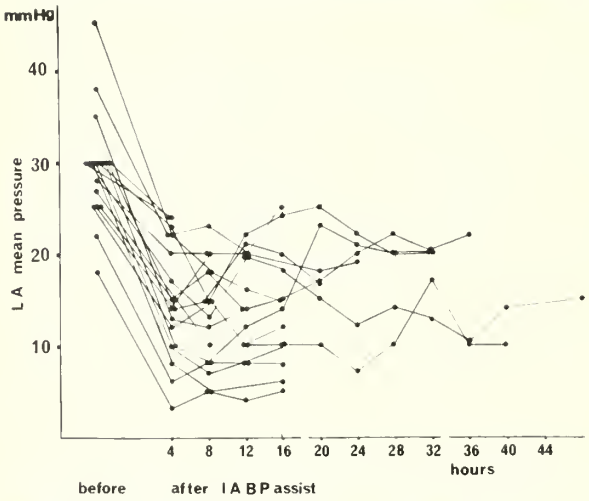

Figure 1.—The serial changes of the mean left atrial pressure during intraaortic balloon pumping (IABP) assist.

operative period, from five hours to two days following return to the intensive care unit. In all of the patients coronary arteriography and left ventricular evaluation were done preoperatively. The ejection fraction was calculated from end diastolic and end systolic volumes, which were obtained by the area-length method of Sandler and Dodge.[2]

Surgical operation in all patients was carried out by means of cardiopulmonary bypass using the profound hemodilution technique as reported previously by Zubiate and co-workers.[3] In 27 patients myocardial revascularization alone was carried out. In seven patients surgical procedures for complications of myocardial infarction were done with myocardial revascularization and in two there was aortic and mitral valve replacement for rheumatic lesions with myocardial revascularization.

The intraaortic balloon pump assist was employed if an adequate circulation could not be obtained when cardiopulmonary bypass was terminated. In Group II the indication for IABP in the early postoperative period was that adequate circulation could not be maintained and the mean left atrial pressure was greater than 25 mm of mercury and the systolic arterial pressure was below 60 mm of mercury despite medical treatment.

The AVCO-IABP system was used in all patients with an average assist of 41 hours, ranging from 15 to 120 hours. Heparin was administered to all patients while on IABP assist, keeping the coagulation time within a range of 15 to 30 minutes. Weaning was accomplished by decreasing the time interval of inflation according to the stability of the clinical finding, blood pressure, left atrial pressure and urine output.

Results

Of the 36 patients in whom IABP assist was applied, 21 survived and were discharged for an overall survival rate of 58 percent.

Of the 31 patients in whom IABP assist was required following cardiopulmonary bypass (Group I), 19 were weaned from IABP. Of five patients who were supported with IABP assist because of refractory cardiogenic shock in the early postoperative period (Group II), three were successfully weaned. One patient died of documented myocardial infarction 11 days after satisfactory cessation of IABP assist.

The preoperative status and the results in the 36 patients are shown in Table 1. Except for the death of one patient due to uncontrollable bleeding while receiving IABP assist, no other major complications could be directly related to IABP assist.

Figure 1 shows the pronounced changes in mean left atrial pressure during IABP assist. Of the 23 patients in whom there was successful IABP assist following cardiopulmonary bypass, left atrial pressure measurements were available in 17 patients. In these patients left atrial pressure decreased significantly in the early period after employment of IABP.

Discussion

Intraaortic balloon pump assist was initially employed for mechanical circulatory aid in the treatment of cardiogenic shock due to acute myocardial infarction. This modality has also

been employed for support following open heart surgical procedures.[4-7] There have been a number of reports on IABP assist for intraoperative myocardial failure following cardiopulmonary bypass.[4-7] In 1973, Buckley and associates[4] reported on a series of 26 patients requiring IABP assist following elective cardiac surgical operation, including operation for valvular heart disease. Seventeen were successfully weaned from IABP assist. In 1973, Berger and associates[5] also reported that 6 of 14 patients survived with the aid of IABP assist following surgical procedures. In our series of 36 patients requiring IABP assist following surgical operation or in the immediate postoperative period, 21 patients survived and were discharged home for an overall survival rate of 58 percent. There was only one late death following successful termination of IABP assist. These results are similar to the reports of others who noted that IABP assist provided time for recovery of depressed left ventricular function due to intraoperative myocardial injury with augmentation of myocardial perfusion and decrease in left ventricular afterload.

Of the present series of 36 patients, in 13 there were extremely poor ejection fractions of 0.1 to 0.2. Nine (69 percent) of these 13 patients survived with the aid of IABP assist. However, only 11 of 23 of the patients with a better ejection fraction of 0.25 to 0.70 survived with the assist device. The explanation for this is not readily apparent, but most likely is as follows. For patients with an ejection time of 0.1 to 0.2 a surgeon is more inclined to use the device sooner since the margin of success in these critically ill patients is so very low. With the first failure to come off bypass, the device is employed in these critically ill patients; whereas, with a better ejection fraction, one continues to attempt to come off bypass and only after many repeated failures is the IABP employed. By this time, the heart has suffered so much injury that the chance of success with the IABP assist device is decreased to a pronounced degree even though the ejection fraction was better before surgical operation.

In three patients, IABP assist was unsuccessful because of intractable ventricular tachyarrhythmia. Sehapayak and associates[8] reported three patients in whom IABP assist was applied in an attempt to treat recurrent ventricular tachyarrhythmia. They suggested that IABP assist was ineffective in controlling this type of arrhythmia. In the report by Berger and associates, there were four deaths due to uncontrollable ventricular arrhythmia.[5]

Anticoagulant therapy was used in all patients. One patient in our series of 36 died from uncontrollable bleeding in the early postoperative period. We encountered no significant complications directly related to IABP assist in the other 35 patients.

During our initial experience the mortality rate was high, but this has improved recently. From our experience it is imperative that in order to obtain more successful results, IABP assist should be instituted without delay, now that its safety and efficacy in supporting the circulation has been well established.

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Refer to: Johnson RH, Krupp JR, Hoffman AR, et al: Nosocomial vaccinia infection. West J Med 125:266-270, Oct 1976

Nosocomial Vaccinia Infection

RUDOLPH H. JOHNSON, MD; JAN R. KRUPP, MD; ANDREW R. HOFFMAN, MD, *and* JEFFREY P. KOPLAN, MD, *Stanford;* JAMES H. NAKANO, PhD, *Atlanta;* THOMAS C. MERIGAN, MD, *Stanford*

Although hospital-associated spread of vaccinia has been reported in the past, there have been no recent reports. This paper describes hospital-associated spread of vaccinia virus infection, supplies data on the environmental survival of vaccinia virus and offers recommendations for the management of patients with vaccinia that may minimize the hazard of infection in other high-risk patients.

THE WORLDWIDE INCIDENCE of smallpox has declined as the World Health Organization eradication program has progressed.[1] In the United States there has been a decrease in the number of yearly smallpox vaccinations and a subsequent decline in vaccination complications. Because of the decreasing threat of smallpox importation[2] the recommended policy of the United States Public Health Service (USPHS) is selective rather than universal vaccination.[3] However, with 6.7 million vaccinations carried out yearly as of 1973,[1] complications of vaccination are still being seen in clinical practice.

Hospital spread of vaccinia is a rare[4-9] but important complication. It is recognized as a possible hazard to inpatients in the current USPHS recommendation[3] and hospital infection control programs. However, there have been no reports in the English language literature documenting this danger in the last ten years.

Reports of Cases

PATIENT 1.—On May 3, 1975 a 19-year-old man, a native of India with a lifelong history of atopic dermatitis, was admitted with the diagnosis of disseminated vaccinia to a dermatology ward and placed in isolation requiring the use of gown and gloves. Although the patient had tolerated a smallpox vaccination without sequelae in 1963, revaccination ten days before this admission resulted in the eruption of hemorrhagic vesicles and umbilicated pustules over the face, neck, arms and thighs. He received 35 ml of vaccinia immune globulin (VIG) in divided doses, and was started on a course of oral erythromycin. Following this therapy the skin lesions crusted and formed scabs. Mild conjunctivitis was treated with topical administration of idoxuridine. On May 8, it was noted that 80 to 90 percent of the vaccinial scabs were gone. Later that day, three hours before discharge, the patient was released from isolation and was seen walking through the corridors of the ward in street clothes.

PATIENT 2.—On April 9, 1975, a 63-year-old woman who had been vaccinated at age 5 and with a history of mycosis fungoides was admitted to the hospital for electron beam therapy. Although the patient was not being treated with chemotherapy at that time, during the previous three years she had been treated with prednisone, Grenz (superficial, poorly-penetrating) ray therapy, methotrexate and topically administered nitrogen mustard. There was diffuse involvement with this cutaneous lymphoma, including bilateral axillary and inguinal lymphadenopathy and circulating Sézary cells. After a left inguinal lymph

From the Division of Infectious Diseases, Department of Medicine, Stanford University Medical Center, and the Center for Disease Control, Atlanta.

Dr. Johnson was supported by an Advanced Research Fellowship from the Bay Area Heart Research Committee, San Francisco. Dr. Koplan was supported by a Career Development Award from the United States Public Health Service.

Dr. Hoffman was a Senior medical student at Stanford University School of Medicine when paper was submitted.

Submitted December 17, 1975.

Reprint requests to: Rudolph H. Johnson, MD, Section of Infectious Diseases, Veterans Administration Hospital, 1030 Jefferson Ave., Memphis, TN 38104.

node biopsy study was carried out, the results of which confirmed the presence of mycosis fungoides, an abscess developed at the incision site leading to staphylococcal and streptococcal septicemia which was treated with parenteral antibiotics. On May 8, Patient 2 was seen in the same hallway where Patient 1 had been walking that afternoon.

Figure 1.—Upper, vaccinia lesions of the hand 18 hours after administration of vaccinia immune globulin (VIG); **Lower,** 96 hours after VIG.

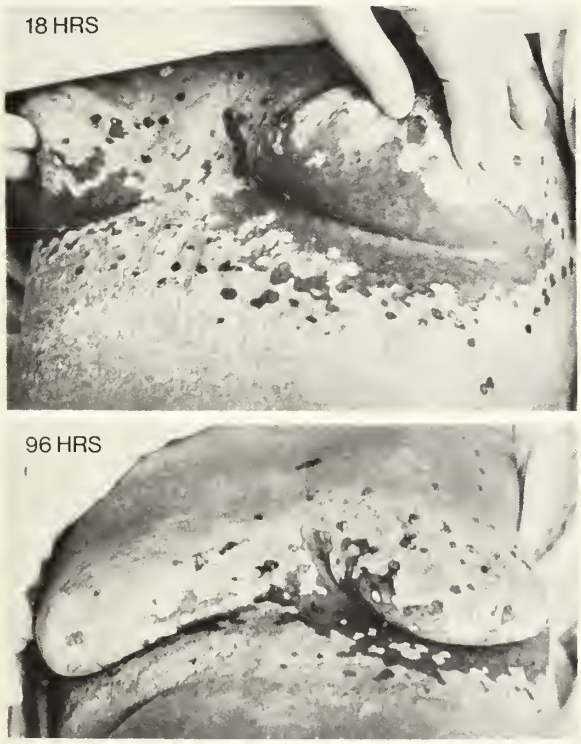

Figure 2.—Upper, vaccinia lesions of the intertriginous areas of the breasts 18 hours after administration of VIG; **Lower,** 96 hours after VIG.

On May 18, after four weeks of antibiotic therapy, Patient 2 again became febrile. Administration of antibiotics was discontinued two days later. On May 20, a massive eruption of 2 to 3 mm, nonpruritic, nontender macules occurred, which evolved into white pustules scattered over the trunk, hands and eyelids. In the intertriginous areas under the breast and in the perineum, the lesions were confluent. The patient noted no systemic and local symptoms. The leukocyte count was found to be 2,700 per cu mm. In the days that followed, many of the pustules umbilicated. Findings on multiple Gram stains, potassium hydroxide preparations, and bacterial and fungal cultures from the lesions were negative. Results of a biopsy study of one of the lesions were considered consistent with viral disease because of the presence of multinucleated giant cells and polymorphonuclear leukocytes in the upper and middermis, and the absence of fungi and bacteria, on periodic acid-Schiff (PAS) and Gram stains.

Figure 3.—Upper, vaccinia lesions of the perineum 18 hours after administration of VIG; **Lower,** 96 hours after VIG. Note the loss at 96 hours of edema of the borders of confluent lesions easily seen at 18 hours after VIG.

Fluorescent antibody (FA) tests of lesion scrapings were negative for herpes simplex and varicella-zoster viruses, but positive for vaccinia virus. Subsequently, tissue culture cells (infant foreskin fibroblasts) inoculated with vesicle fluid grew out vaccinia virus identified by a direct FA test. The indirect fluorescent vaccinia antibody titer was 1:256.

Subsequently, 0.6 ml per kg of body weight (32 ml) of vaccinia immune globulin was administered in divided doses. Significant crusting of the lesions was seen within 18 hours (Figures 1-3, upper) and further resolution was seen at 96 hours (Figures 1-3, lower). Because of the patient's presumed altered-immune, high-risk status, an additional 16 ml of vaccinia immune globulin was administered. After seven months, Patient 2 remains free of evidence of vaccinia virus infection.

Epidemiology

Patients 1 and 2 were seen in the same hallway at different times on May 8; their respective rooms were 75 feet apart. The isolation rooms in the hospital have double doors and are vented to the outside. The six-bed room that patient 2 shared with three other patients before isolation was not vented to the outside. Patients 1 and 2 never shared skin creams, blood pressure cuffs or other fomites.

In the case of Patient 2, a course of electron beam therapy and whirlpool therapy had been completed on May 17. On May 19 an x-ray study of the chest had been made and the patient was placed in a private room. Between May 18 and May 23 she was febrile and new skin lesions developed, but she was not put in isolation. On May 23, when the fluorescent antibody test was positive for vaccinia, Patient 2 was isolated with glove, mask, cap and gown precautions, and the entire ward was closed to new admissions. Two of Patient 2's previous roommates were immunosuppressed patients; they were placed in separate single rooms and vaccinia immune globulin was administered. The third roommate had psoriasis and had been discharged; she was recalled to the hospital and vaccinia immune globulin was given. The Hubbard tank and tub room, the x-ray room and the electron beam therapy rooms were decontaminated with Chlorox® (5.25 percent sodium hypochlorite) solution (1:20).

There were 106 people identified as possible contacts of one or both patients. These contacts were distributed among various hospital personnel groups. The husband and roommates of Patient 2 before her isolation were also included. Of 106 possible contacts, 31 were initially found on brief interview to have been at close contact with either Patient 2 alone (19/31) or both Patient 2 and Patient 1 (12/31).

Of the close contacts, 30 were interviewed in detail with a questionnaire. In all 30, blood specimens were taken on two occasions in June, separated by two to three weeks; no viral culture studies were attempted. No fever or skin rash developed in any of the 30 persons after contact with these patients. All had been vaccinated against smallpox in the past and nearly all had visible vaccination scars, but none who cared for Patient 1 or Patient 2 had been recently vaccinated.

Paired sera were selected from among the 30 close contacts on the basis of established contact with both patients. The sera were from seven nurses, one nursing assistant and two physicians. Paired sera were examined for evidence of significant rise in antivaccinia titer by means of complement fixation (CF),[10] hemagglutination inhibition (HI),[11,12] viral neutralization[13] and radioimmunoassay[14] tests. The results were unremarkable for HI and CF tests. Both members of each pair were positive with the radioimmunoassay and the neutralization tests. These results do not suggest recent infection but are consistent with previous vaccination.

Because of the possibility of transmission of vaccinia virus by means of environmental fomites, including hospital walls, and because there are no data in the literature on the environmental survival of vaccinia virus, studies were done to evaluate the possibility of environmental transmission of vaccinia.

Using a 19-gauge hypodermic needle, four drops of a dried calf-lymph smallpox vaccine, reconstituted and previously titered to contain $10^{6.9}$ pock-forming units per 0.1 ml, were placed on each of ten cleaned glass slides. The slides were dried and left in a decontaminated hood at a temperature of approximately 75°F (25°C).

The dried vaccine material on each slide was reconstituted with four drops of sterile, distilled water, using a 19-gauge hypodermic needle. A drop of the reconstituted material on each slide was inoculated onto each of the two chick chorioallantoic membranes (CAM) to quantitate the surviving virus. The results (Table 1) indicate

TABLE 1.—*Survival of Vaccinia Virus in a Reconstituted Smallpox Vaccine, After It Was Placed on Slides, Dried and Left at Room Temperature (About 25°C or 75°F)*

Hours Left at Room Temperature	*Growth on Chorioallantoic Membrane**
0	Confluent
2	Confluent
4	Confluent
6	Confluent
10	Confluent
27	Confluent
30	Confluent
52	Confluent
78	Semiconfluent
144	Negative

*Inoculum = 1 drop through a 19-gauge hypodermic needle.

that vaccinia virus dried at room temperature and left at room temperature in a normal room environment was viable in large enough numbers at 78 hours that a drop of suspension gave semiconfluent growth on the CAM. However, no live virus titer was detectable at 144 hours. A noticeable decrease in live virus titer apparently began after 52 hours.

Discussion

It has generally been assumed that epidemiologic and other features of smallpox[15] apply to vaccinia. Currently there is insufficient information to confirm or negate the validity of this assumption.

Environmental Survival and Potential Transmission of Vaccinia Virus

Hospitals have been a frequent site for outbreaks of smallpox.[15] There have been several sporadic reports of vaccinia virus transmission within a hospital (for examples, see references 4-9). Five of the six cited epidemics were in dermatologic infirmaries or wards.[4-6,8,9] Findings in four of these reports were confirmed by modern virologic studies[6-9] and in two were suspected on clinical grounds.[4,5]

The spread of vaccinia virus infection is generally believed to require person-to-person contact[9,16] and has been seen in familial settings.[16,17]

The transmission of infectious vaccinia virus by fomites has not been shown to occur. However, Koplan and Marton[18] were able to culture virus from vaccinia scabs and from scab sites after the scabs had fallen off. Smallpox virus has been recovered from bedclothes, pillow swabs and back swabs of smallpox patients.[19] The results of this study show that infectious vaccinia virus in the absence of scabs may persist in the environment for three to four days. Whether vaccinia virus infection can be transmitted this way is presently unknown but our data suggest this possibility.

Epidemiologic Evaluation of the Transmission of Vaccinia from Patient 1 to Patient 2

The clinical diagnosis of vaccinia virus infection may be extremely difficult in the absence of a suggestive history, as the differential diagnosis of nonbacterial pustular dermatoses involves many different etiologic possibilities.[20] The diagnosis of vaccinia virus infection in Patient 2 was complicated by the initial absence of a suggestive history, and obscured by the underlying cutaneous lymphoma in this patient. However, when the clinical diagnosis of vaccinia was considered, it was rapidly confirmed by the fluorescent antibody test of vesicle scrapings, and the virus was grown in tissue culture subsequently. Therapy with vaccinia immune globulin was promptly initiated and such therapy may have been lifesaving. It is well-recognized that infection is the most common cause of death in patients with mycosis fungoides.[21]

Others at risk of acquiring clinically significant vaccinia infection include those with eczema or other chronic dermatoses, those with an acquired or inherited immune deficiency state, fetuses of pregnant patients and children younger than 12 months of age.[1]

The serologic data of the contact persons failed to show any recent vaccinia infections among them. It should be noted that Patient 1 was admitted to hospital May 3, and stayed until May 8; if infection of hospital personnel occurred during this time, the shortest interval between the time of infection and the time of collection of acute phase blood specimens was May 8 to June 10 (33 days). This interval is sufficient to produce a rise in antibody titers in a person in whom an asymptomatic vaccinia infection has developed. There is a report that serologic responses to smallpox antigens have been detected in asymptomatic contacts of overtly ill smallpox patients.[22] Since no isolation of virus was attempted in our study, it is possible that asymptomatic infection (for example, with pharyngeal excretion of virus) developed among one or more hospital personnel and accounts for spread of vaccinia virus from Patient 1 to Patient 2.

Pharyngeal excretion of vaccinia virus has been shown to occur in 18 of 80 vaccinated children.[23]

This was generally within the period of 6 to 12 days following vaccination, but as long as 20 days after vaccination in one case. Pharyngeal and urine viral cultures were negative for vaccinia virus in the study of Koplan and Marton[18] in each of eight volunteer vaccinees on days 2, 4, 7 and 10 postvaccination. Pharyngeal excretion of vaccinia virus has not been documented as a clinically significant means of vaccinia virus transmission.[23]

The structure of the double-doored isolation rooms with venting directly to the outside makes airborne spread of vaccinia virus unlikely in this hospital situation. However, airborne spread of smallpox infection within a hospital has been described.[24]

Two more plausible modes of transmission of vaccinia virus in this epidemiologic setting are by means of (1) either unrecognized fomites (such as creams, instruments, bed clothing) or other inanimate objects (such as walls) in the corridor of the ward where both patients were seen and (2) direct contact from first patient to hospital personnel to second patient. In the absence of clearcut information implicating the sharing of common body creams, instruments, bed linens, or other fomites, the most likely mode of transmission of vaccinia virus between these two patients is by direct contact from hospital personnel. However, it is also possible that Patient 2 became infected on May 8 by means of vaccinia virus on fomites in the hall visited by Patient 1 on the same day.

Recommendations for the Management of Patients with Vaccinia Virus Infection

From this experience with in-hospital transmission of vaccinia virus infection, several recommendations for the isolation and care of vaccinia patients may be formulated. (1) Hospital admission offices should consult the infection control nurse or hospital epidemiologist before admitting any patient with a diagnosis of vaccinia. (2) Patients with vaccinia virus infection should not be admitted to dermatology or other wards that contain high-risk patients, but should be managed either as outpatients, or admitted to a ward where minimum exposure to patients at risk can be assured. It is significant that several previously described nosocomial outbreaks of vaccinia virus infection occurred in dermatology wards.[4-6,8,9] (3) A patient isolated for vaccinia virus infection should be treated with vaccinia immune globulin (VIG) and discharged directly from the hospital. (4) Hospital personnel caring for patients with vaccinia virus infection should not work concomitantly with patients at high risk of acquiring vaccinia. (5) Hospital personnel should be alerted to the possibility of secondary cases of vaccinia virus infection, because the longer an undiagnosed patient remains unisolated, the greater the danger to other high-risk patients. (6) Recently vaccinated hospital personnel should be made aware that they are a potential hazard to high-risk patients because of the persistence of vaccinia virus at the vaccination site.[18]

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Pressure Gun Injection Injuries of the Hand

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Pressure gun injection injuries are becoming increasingly common. Their effect on the fingers and hands, especially when improperly managed, can be devastating. Therefore it is important to review features, clinical course, anatomic distribution and operative management of such injuries. If a useful hand and fingers are to be attained, rapid and thorough decompression and debridement of these injuries are essential.

PRESSURE GUN injection injuries involve the injection of an industrial substance, usually paint or grease, into the hand at pressures ranging from 750 pounds per square inch to 12,000 pounds per square inch. The object of this review is to further publicize this type of injury and to emphasize the extreme urgency of appropriate surgical care. Pressure gun injection injuries have received emphasis in the surgical literature, major articles being those by Stark and co-workers[1,2] and Waters and co-workers,[3] but there are still too many cases in which necessary treatment is delayed.

Recognition of the potential severity and urgent nature of paint or grease gun injuries is the key to successful management.

Rees, in 1937, was the first to describe this injury. Scattered case reports have accumulated since then, and there are now approximately 100 cases reported in the literature. However, these injuries are much more common than the number of reports would indicate and as industry finds more uses for high pressure airless guns, it seems likely that more of these injuries with a wider range of injected materials will be seen.

Pressure gun injuries fall into two categories, distinguished by different clinical courses. The most commonly injected substances are paint and related solvents, stains and thinners.

Water-base paint is the least locally toxic of the common paints, followed by roofing paints and other types of outdoor paints, and the most toxic substance is turpentine. These are complex chemicals, not amenable to neutralization nor dissolution. The injuries caused by paint are characterized by a very intense initial inflammatory reaction. Minimal delay is the key to a successful outcome in the management of paint gun injuries. If decompression and debridement is carried out within four hours of injury, the prospect for attaining a functioning hand is fairly good. If 12 hours or more has passed since injury, the functional results are usually poor and serious consideration should be given to primary amputation of the involved digit.

The second category of pressure gun injuries involves grease guns. These injuries are characterized by a less intense initial inflammatory reaction, but by more frequent delayed abscesses and more residual fibrosis.

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The management of these injuries in the 1940's and 1950's was nonoperative, with the usual result being amputation. It gradually became appreciated that operative removal of the injected material was the only way a functional finger or hand could be obtained. Delayed surgical care yields a result similar to nonoperative management.

The reason that prompt surgical decompression and debridement is essential is the rapid onset of severe ischemia in the injected finger. The development of ischemia is much more pronounced in pressure gun injuries involving paint than in those involving grease.

If a paint gun injury is seen 30 to 60 minutes after injection, the entrance wound will be a small puncture site and the finger will not be greatly swollen or painful, and will probably have a nearly full range of motion. The same finger an hour or two later will have become painful and swollen, and significant cyanosis will have developed. The benign appearance of the early injury, of course, is responsible for the fact that the severity of the injury is often not appreciated. When it becomes apparent to the patient that the condition of the injured finger is deteriorating, much of the damage is already irreversible.

It seems likely that the basic cause of the ischemia is the rapid development of severe edema secondary to the inflammatory response to the foreign material. It is the decompression of the swollen finger that is at least as important as removal of the foreign material. An additional cause of digital ischemia is the frequent occurrence of thrombosis of one or both of the digital arteries.

Anatomy

The distribution of the injected substance is determined by a combination of the pressure of injection and the fascial planes of the finger and hand. At the site of injection and around it, the injected substance will permeate all the tissue. The neurovascular bundles in the area will be completely infiltrated. The infiltration of the nerve with the injected substance accounts for the hypesthesia often noted on initial examination of pressure gun injected fingers. This initial absence of pain may further mislead the initial examiner

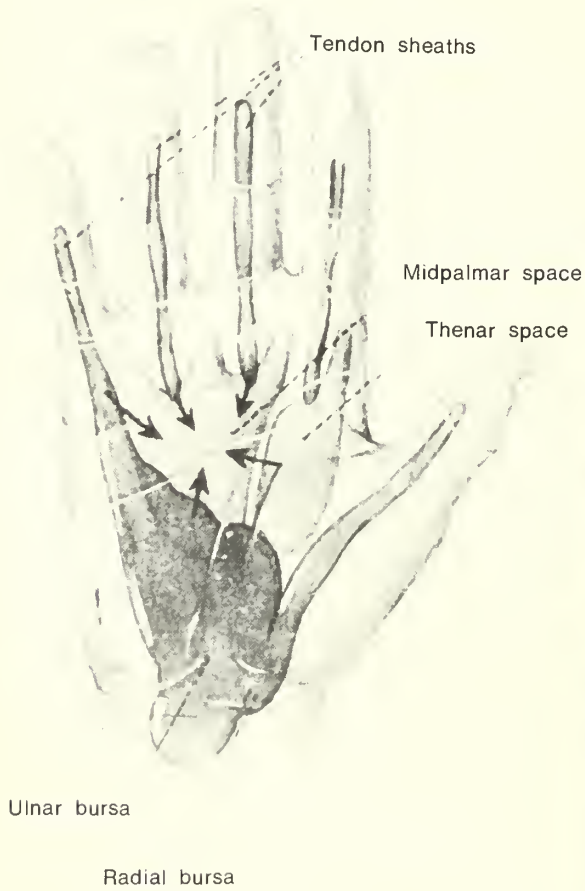

Figure 1.—The location of tendon sheaths and bursae in the hand which may be involved in a pressure gun injury.

Figure 2.—A photograph illustrating the early benign appearance of a paint gun injury.

into underestimating the severity of the wound.

Involvement of the tendon sheath presents a severe problem because its involvement nearly assures residual stiffness. Experimentally it has been found that the thinner portion of the sheath, over the phalangeal flexion creases, is readily penetrated and if the site of injection is over the flexion creases, flexor tendon sheath involvement is likely. The thicker portions of the sheath over the shafts of the phalanges are not so readily involved. In the operative management of this injury the sheath should be opened sufficiently to determine whether or not involvement is present.

The course of the injected material, after leaving the finger, depends mostly on which digit is injured (Figure 1). In the thumb the material often involves the thenar muscles with greater or lesser damage. If the flexor pollicis longus tendon sheath is involved, the substance may enter the radial bursa and consequently involve the structures in the carpal canal, or can enter the retroflexor space of Parona in the wrist, or finally can enter the ulnar bursa and involve the flexor tendon sheath of the fifth finger in a retrograde manner. Therefore, operative management of an injection injury to the thumb may necessitate a carpal tunnel decompression.

Figure 3.—An x-ray film of the left ring finger shown in Figure 2. It shows the proximal and distal spread of the paint that would certainly be unexpected from the clinical appearance.

Injection of the index finger, probably the finger most commonly involved, may extend into the subcutaneous tissue of the palm and if the flexor tendon sheath is involved the thenar space may also become involved. Similar patterns of distribution are seen in the long and ring fingers. However, if the flexor tendon sheaths are involved the injected material will spread to the midpalmar space. In the case of the long and ring fingers, as well as the index, the force of injection can be sufficient to drive the paint into the carpal canal. Appropriate operative management dictates pursuit of the injected material as far as it appears to go. Finally, the possible distribution of the injected substance in the little finger is analogous to the pattern in the thumb; the hypothenar muscles can be injured and the spread may be into the ulnar bursa, space of Parona and the carpal tunnel.

Clinical Presentation

The typical case is that of a young man whose paint gun has malfunctioned and who wipes off

Figure 4.—The limited incision and drainage that had been carried out for a paint gun injury in Case 1.

the tip of his airless paint gun with the tip of the index finger of his nondominant hand. Initially the finger wound will appear as a pinpoint defect and the finger will not be especially swollen or painful (Figure 2). A close to normal range of motion will be present and there will be no systemic symptoms. With prompt surgical management the progressive deterioration of the finger and hand will be aborted. However, systemic symptoms and laboratory evidence of inflammation may be seen for the first two to four postoperative days. This usually does not mean that the hand has become secondarily infected, although a close watch for infection must be maintained. These signs and symptoms are usually a manifestation of chemically-induced inflammation in the tissues.

In contrast, systemic toxicity is not usually seen after adequate surgical care in a finger or hand injected with grease. Should an elevated leukocyte count, fever, axillary or epitrochlear adenitis, or lymphangitis develop postoperatively in a patient with a grease gun injury, a search for a hand abscess must be made.

Another presentation of the problem is seen much too often. The typical patient is a young

Figure 5.—The extensive spread of the paint through the radial half of the hand in Case 1.

Figure 6.—Plastic injection into the thenar eminence in Case 2.

Figure 7.—The spread of plastic into the dorsum of the hand, wrist and distal forearm in Case 2.

man who has sustained a paint gun injury to his finger or hand. After a brief examination in an emergency room or his family physician's office, a tetanus shot is given, antibiotics prescribed and the patient told to soak his hand. The patient then usually waits about 24 hours, until the injured finger has become inflamed and swollen and the pain is excruciating, and then returns for further examination. By this time a portion of the volar skin usually has become necrotic, massive edema has been established and considerable soft tissue necrosis within the subcutaneous tissue, and possibly the palm, has occurred. The operative management of this problem is the same as in the acute injury, but the results are much less satisfactory.

Management

As mentioned, recognition is the first and most important element in the proper management of these injuries. The speed with which the patient is taken to the operating room and the paint or other material removed is the key to successful management.

The history obtained from the patient should include hand dominance, occupation, material injected, time of injection, pressure of injection, any previous therapy and circumstances surrounding the injection injury. In addition, other pertinent historical information should be noted and the usual systemic review made. Physical examination should include determining the range of motion of the hand and involved finger, how sensitive they are and especially their vascular status. If there has been any previous therapy it should be determined if a digital block was given. Frequently it is found that a digital block has been given for pain relief. This is felt to be contraindicated and associated with a worsening of the vascular status of the injured digit.

Figure 8.—The eventual outcome in Case 2 following multiple reconstructive procedures.

X-ray studies should be carried out in order to find the extent of spread of the injected material (Figure 3), as well as to discover any associated injuries. Many injected substances, including water-base paints, have sufficient impurities to show on radiographs. Therefore, for example, if paint is noted in the palm on an x-ray study in the case of a fingertip injection injury, this would discourage the local incision and drainage sometimes done for such injuries.

Until an operating room is available, intravenous administration of antibiotics, appropriate tetanus immunizaton and elevation of the injured hand should be carried out. An important part of the preoperative preparation is informing the patient that his rather benign appearing wound is indeed a severe injury and will cause a significant period of disability and possibly the loss of all or part of the injured fingers.

Operative management requires adequate anesthesia, either general or axillary block, and tourniquet control of bleeding. If a finger is involved, it is exposed through a mid-lateral incision. This incision affords exposure of both the dorsal and volar aspects of the finger, and if a skin graft is required for secondary closure, as is often the case, the graft is then in a nonpressure area. As much of the paint or other material as possible is then meticulously removed; this requires a combination of sharp debridement and irrigation. (Unfortunately, there is no solvent available for any of the usually injected materials that is any less toxic to the tissues than is the original injurious material.) The Water Pik® type of irrigator is often a great help. The neurovascular bundles are usually densely infiltrated and should be cleaned as thoroughly as possible. The tendon sheath should be opened just enough to ascertain whether or not it is involved. If it is, the entire sheath should be removed, leaving only

the pulleys at the middle and proximal phalangeal levels. Generally the palm should be opened and carefully inspected for involvement.

Following as complete a debridement as possible, the wounds are usually left open and on occasion a small irrigating catheter is left in the tissues for 48 to 72 hours and normal saline solution instilled in the hope of further mechanical removal of injured tissue and the injected material. Postoperatively the hand should be kept bandaged, splinted and elevated for four to five days. After this period, attention should be given to regaining and maintaining as much range of motion in the involved digit and hand as possible.

The tissue reaction is slow to subside, especially in cases in which treatment has been delayed, and the fingers may remain swollen and tender for two to three weeks. If early motion is not encouraged, an injured finger would become hopelessly stiff by the time all the edema subsided. Because of the delayed resolution of the tissue reaction, final closure of the skin defect is often not done until two to three weeks following the injury. It is at this point that a very careful appraisal of the patient (including a consideration of his occupation and motivation) and the injured finger must be made. In some cases, again especially those in which treatment was delayed, a partial or complete amputation may rehabilitate the patient and allow him to return to work much more expeditiously than any continued attempts to reconstruct the injured finger.

Some examples illustrate typical problems encountered in the care of patients with such injuries.

Reports of Cases

Case 1. The first case is that of a young man who received a paint gun injury to his right index finger over the volar aspect. Figure 4 shows the limited incisions made in an emergency room before the patient's transfer. Figure 5 shows the extensive spread of the paint into the thenar space, the thenar musculature and the carpal canal. The paint involved both neurovascular bundles to the index with thrombosis of both digital arteries, there was destruction of most of the thenar musculature and there was considerable involvement of the median nerve in the carpal canal. Eventually a Ray resection of the index finger was carried out and satisfactory results were achieved.

Case 2. This case illustrates the terrific damage that can be inflicted by a pressure gun injury and further points out the increasingly widespread use of pressure guns in industry. The injury to this patient resulted from injection into the thenar eminence with plastic at a temperature of 400°F (Figure 6). Figure 7 shows the spread of the plastic into the dorsum of the hand, wrist and distal forearm. The injected plastic destroyed a portion of the thumb metacarpal, a portion of the carpus and all tendons and nerves in its path. Figure 8 shows the eventual outcome following multiple reconstructive procedures.

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Medical
PROGRESS

Orofacial Dyskinesia

Clinical Features, Mechanisms and Drug Therapy

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Orofacial or tardive dyskinesias are involuntary repetitive movements of the mouth and face. In most cases, they occur in older psychotic patients who are in institutions and in whom long-term treatment with antipsychotic drugs of the phenothiazine and butyrophenone groups is being carried out. These dyskinesias are frequent in occurrence and characteristically are irreversible. Several biochemical mechanisms have been proposed as causes, including hypersensitivity or partially deneverated brain dopamine receptors and low affinity of the offending drugs for brain muscarinic cholinergic receptors. Clinical therapy has been attempted primarily with drugs that antagonize dopamine receptors or deplete brain dopamine. The benefits of drug treatment have been variable and lack of consistent improvement has been discouraging. Early recognition of dyskinesia should be attempted, and the dose reduced or the drug omitted at the first sign.

DRUG THERAPY of certain disorders, especially treatment of schizophrenia with phenothiazines and parkinsonism with L-dopa, has been associated with the emergence of certain abnormal involuntary movements termed dyskinesias.[1-4] These are involuntary, repetitive and stereotyped movements, involving the head, face and oral structures. In their typical presentation, tardive or orofacial dyskinesias consist of tongue protrusion with licking of the lips, sucking and smacking movements with the lips, chewing movements, grunting and similar sounds, puffing of the cheeks, forehead furrowing and eye opening and closing. In many cases, the limbs and trunk are also involved. When drug-induced, these manifestations may appear at any point during the drug treatment, including while the drug is being given, after termination of treatment or upon reinstitution of treatment. In many cases, the dyskinesias persist for months or years and there is poor response to drug manipulation or they are irreversible. The significance of orofacial dyskinesias is underscored by the fact that these now appear to be the major side effect limiting the use of the antipsychotic drugs, which are currently the most frequent cause of dyskinesia. Similar movements were reported to occur following epidemic en-

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cephalitis in the first part of the 20 century[5] and as being among the clinical features of certain basal ganglia disorders such as Huntington's chorea,[6] Sydenham's chorea[7] and Wilson's disease.[8]

This review will focus on clinical characteristics, basic mechanisms and therapeutic approaches. Drug-induced dyskinesias will be stressed because drugs are at present the most frequent cause of dyskinesias. The major responsible drugs are the phenothiazines and butyrophenones,[9] which are the two main classes of antipsychotic or neuroleptic agents (defined as drugs that cause psychomotor slowing and emotional quieting). Since the available literature on orofacial dyskinesias has grown enormously in recent years, the emphasis will be on concepts and therapeutic approaches rather than comprehensive citation of all the reports.

Clinical Features

A variety of terms have been applied to these involuntary dyskinetic movements, including tardive dyskinesia, orobuccolingual dyskinesia, facial dyskinesia, extrapyramidal insufficiency syndrome, drug-induced dyskinesia, cephalic dyskinesia and dyskinetic syndrome. Tardive dyskinesia, the first of these terms, was applied at first to abnormal orofacial movements that appear only following a long course of treatment or even after the discontinuation of therapy with the implicated drug, and hence the designation that the dyskinesia is "tardive."[2] However, because in some cases the dyskinesia occurs even in the early phases of the administration of the offending drug or the history of drug exposure is uncertain, it may be more appropriate to use the broader term of orofacial dyskinesia, since this denotes both the topography of involvement as well as the type of abnormal movement. Most cases of dyskinesia are drug-induced; however, in some cases there is no history of drug exposure. Of this latter group, in some patients there is a history of brain damage, electroconvulsive therapy (ECT) or previous surgical operation involving the brain, while relatively few of the cases are idiopathic. In many cases, the orofacial dyskinesia is accompanied by cervical or truncal dyskinesias (including involvement of respiratory function) and limb dyskinesias, including choreoathetosis, ballismus, myoclonus, dystonia, and restless legs (akathisia). However, the orofacial component is often the most disturbing to the patient and to the family for several reasons. Besides the obvious cosmetic disfigurement, orofacial involvement may significantly impair the important functions of eating, speaking and in some cases breathing.[10] These movements appear to be a common expression of a diverse group of disorders and occur in patients in whom dyskinesia is part of a more generalized disorder or in whom it is the major if not solitary manifestation. Thus it may be most appropriate to view orofacial dyskinesia as part of a symptom complex rather than as a specific expression of particular diseases.

The clinical history of this disorder, including incidence, predisposing factors, spontaneous remissions and responsiveness to drugs is not fully known and is disputed at best. The reported frequency of occurrence has ranged from as little as 0.5 percent of patients being treated with phenothiazines to as high as 41 percent.[11] There was an overall 17.6 percent incidence in a review of 22 reported series involving 22,399 patients treated with neuroleptics.[11] Several factors that may account for this discrepancy include variable definition of the syndrome and differentiation from other extrapyramidal syndromes, differing patient populations (especially regarding drug usage) and different techniques of assessing clinical status. A recent estimate suggests that drug-induced dyskinesias occur in 3 to 6 percent of psychiatric patients and in approximately 20 percent of elderly patients who are long-term or frequent residents of institutions.[12]

Orofacial dyskinesias should be clearly differentiated from other abnormal movements, especially those arising after exposure to neuroleptic drugs. Other extrapyramidal syndromes are acute dystonic reaction, drug-induced parkinsonism and akathisia.[2,12] Acute dystonic reactions typically occur in younger rather than in older patients and in males more than in females. Since they appear within a day or two of initial drug use, they reflect individual sensitivity to the drug used and respond promptly to parenteral administration of antihistamines or antiparkinsonian agents. Drug-induced parkinsonism is characterized primarily by rigidity, tremor and bradykinesia rather than by hyperkinesia, and is reversed by discontinuing administration of the drug or reducing the dose. Akathisia or the "restless legs" syndrome is characterized by an uncontrollable state of constant motion consisting of relentless pacing (tasikinesia) or repetitive movements espe-

cially of the legs, such as foot tapping or alternate adduction and abduction. This condition usually responds to a reduction of drug dosage or addition of a sedative. The relative incidence of the different extrapyramidal complications has been reported as parkinsonian in 38 to 48 percent, orofacial dyskinesia in 41 percent and akathisia in 22 percent of the patients receiving long-term therapy with trifluoperazine.[13] Of a series of 3,775 phenothiazine-treated patients, akathisia was noted in 21 percent, parkinsonism in 15 percent and dyskinesia in 2.3 percent.[14] However, this last category combined cases of acute dystonic reaction with those of orofacial dyskinesia. Despite this grouping, these results serve to suggest a low occurrence rate for these two side effects.

It has been suggested that underlying brain damage predisposes to orofacial dyskinesia.[15] Furthermore, most neuroleptic-induced dyskinesias occur in chronic schizophrenics receiving long-term pharmacotherapy, many of whom have been treated in the past with leukotomies or electroconvulsive therapy. Dementia has been associated with drug-induced dyskinesias and has been suggested to support the role of underlying brain damage. In one series, all 13 women with phenothiazine-induced dyskinesia were demented.[16] Of 29 cases related to phenothiazine and reserpine treatment, 12 (or 41.3 percent) were either demented or had a history of organic brain damage.[17] By contrast, the occurrence of dementia was not statistically increased in 213 patients with with dyskinesia.[18] In this last series, the overall incidence of dementia in 45.5 percent of the total of 683 patients studied appears high, especially since patients from the "subnormal ward" were excluded. No relationship between dementia and dyskinesia was observed in a nursing home population in which dementia occurred in 36 percent of those with dyskinesia and in 33 percent of those without dyskinesia.[19] No relationship was shown between dyskinesia and a variety of brain lesions, including head trauma, central nervous system infections, vascular disease, underlying medical diseases or treatment with ECT or insulin shock.[20] Therefore, it seems that brain damage is not a prerequisite to drug-induced dyskinesias.

The fact that most cases of dyskinesia have been reported in patients with chronic psychosis or dementia indicates that these are the patients who receive long-term therapy with neuroleptic drugs. There is no evidence indicating that chronic psychosis is a prerequisite or plays a specific role in the dyskinesias. This is supported by the reports of dyskinesia occurring in nonpsychotic patients treated with neuroleptics for personality disorders, psychoneurosis, gastrointestinal symptoms and chronic pain.[2,20-23]

Other forms of psychiatric treatment that alter brain function have been studied for possible causal association. A two-fold increase in the incidence of drug-induced dyskinesias was reported in 127 patients who had received electroconvulsive therapy compared with that in 86 patients who had not.[2] By contrast, no definite relationship between orofacial dyskinesia and electroconvulsive therapy could be shown to exist in 214 cases when compared with 468 other cases in which electroconvulsive therapy was not used.[18]

Prefrontal leukotomy in 105 patients was not reported to predispose to dyskinesias.[2,18] Insulin coma treatment in 55 patients was associated with an incidence of drug dyskinesia lower than that in patients who did not receive such treatment.[18]

Assessment of the role of brain damage in the production of dyskinesias may also be approached by neuropathologic examination. In the largest series, brains of 28 patients with dyskinesia were compared with those in 28 controls matched for diagnosis (15 with schizophrenia, 8 with senile dementia and 4 with other forms of psychoses).[24] Of the dyskinetic group, degeneration of substantia nigra cells was seen in 27, compared with only 7 in the control series. Gliosis of the midbrain and brainstem was found in 25 of the dyskinetic group but in only 4 of the control group. In a report of two cases, gliosis of the caudate nucleus together with nerve cell satellitosis and neuronophagia was noted.[25] In contrast to the pronounced differences reported in these two series, no specific lesions were found in the brains of three dyskinetic patients.[26] These neuropathological studies suggest that there is a higher incidence of neuropathologic change in the striatal nigral pathway, and this may predispose to neuroleptic-induced dyskinesias, but the evidence is not conclusive.

Brain damage appears to predispose to L-dopa-induced dyskinesias—L-dopa being the major drug besides neuroleptics associated with orofacial dyskinesia. Dopa-induced dyskinesias have been observed only in parkinsonian patients and never in control patients given L-dopa.[27,28] However, control patients have not been exposed to prolonged high dose treatment and may not be directly comparable to parkinsonian patients.

Age appears to be an important factor, with a higher incidence reported in older patients. In one series of 910 cases, the incidence of drug-induced dyskinesias in those under 50 years of age was 3.8 percent of males and 13 percent of females, while in those over 50 years of age, the incidence rose to 20 percent of men and 35 percent of women.[18] Similar results were reported for a series of 398 patients, in which less than 5 percent of those under 44 years but 33 percent of those older than 65 years were found to have dyskinesia.[11]

Women are affected more often than men by neuroleptic induced dyskinesias, with reported ratios of 2 to 1 up to 5 to 1.[13,16,18] Other reports suggest an equal incidence between the sexes.[11,29,30] It has been suggested that the apparently higher incidence in women actually reflects the increased number of older women receiving neuroleptics in institutions.[31] Of interest is the higher incidence of more severe cases among women as shown when mild or doubtful cases are eliminated.[13] These results are summarized in Table 1.

Administration of drugs for increasing periods appears to increase the risk of dyskinesias. In a series of 109 cases, the incidence was 2.7 percent after less than six months of treatment, 5.5 percent after six months to a year of treatment, 29 percent for one to three years of treatment and 31 percent for more than three years of treatment.[2] These results suggest that with continued therapy the risk of dyskinesias developing does not increase appreciably after the first year of therapy. Similar results have been reported more recently in a series of 85 neuroleptic-treated patients, all over 65 years of age, who were studied in three groups.[11] Of 28 patients treated for six months, in only two, or 7.1 percent did dyskinesias develop. Of those treated for more than five years, the incidence rose to 29 percent. No dyskinesias developed in nontreated patients.

In addition to appearing during continued therapy, dyskinesia may develop for the first time after therapy with the associated drug is stopped. Dyskinesia appearing for the first time was observed in 30 percent of 53 patients with chronic schizophrenia in whom long-term neuroleptic therapy was suddenly stopped in a double-blind study.[31] Furthermore, in all of the patients with dyskinesia during therapy there was an intensification when therapy was discontinued.[31] A recent review indicates that in 5 to 40 percent of asymptomatic patients dyskinesias develop upon discontinuation of chronic antipsychotic treatment.[11] In an attempt to reduce the risk of tardive dyskinesia and to increase recognition in latent cases, it has been recommended that in cases of patients with chronic psychoses administration of antipsychotic medication should be periodically stopped (considered a "drug holiday").[12]

Increased incidence of dyskinesias with longer treatment periods has also been documented for L-dopa-induced dyskinesia; these include orofacial as well as cases with limb and truncal involvement. After one month of dopa therapy, the incidence was 17 percent and this increased progressively with each month of treatment up to 73 percent at 12 months.[10] Increased doses appear to increase the incidence of dyskinesia, which occurred in 9 percent of patients receiving 2 grams per day and rose to 44 percent of patients receiving 7½ grams per day.[32]

Orofacial dyskinesias have been reported to occur with the use of virtually all the antipsychotic drugs, including the phenothiazines and butyrophenones. In one series, the maximum incidence was 25 percent of those receiving chlorpromazine, with an incidence of 13 percent of these receiving

TABLE 1.—*Incidence of Dyskinesia According to Sex*

	Males			*Females*		
Source	*Number with Dyskinesia*	*Total Number*	*Percent with Dyskinesia*	*Number with Dyskinesia*	*Total Number*	*Percent with Dyskinesia*
Hunter (1964)[16]	0	200	0	13	250	5
Degwitz (1967)[20]	33	619	5.3	97	672	14
*	14	619	2.3	65	672	9.6
Brandon (1971)[18]	65	426	15	148	484	30
*	17	426	3.9	73	484	15
Kennedy (1971)[13]	17	32	53	22	31	71
*	8	32	25	18	31	58
Fann (1972)[30]	49	144	34	24	57	42
Crane (1973)[11]	27	210	11	23	138	14

*Mild and doubtful cases eliminated.

haloperidol and thioridizine, and 19 percent of those receiving perphenazine and prochlorperazine.[2] Of 63 patients on trifluoperazine for an average of 9.4 years, definite orofacial dyskinesia developed in 41 percent.[13] Treatment in high dosage may increase the incidence of dyskinesia, as suggested by the findings in a study of 175 patients treated with trifluoperazine. At high doses (80 mg per day) for five months, orofacial dyskinesia developed in 26 percent of treated patients, while low dose treatment (16 mg per day) was associated with only a 4 percent incidence.[29] These results take into account an incidence of 17 percent of dyskinesias in placebo treated patients. Similar results, with dyskinesia appearing in 25 percent, were noted when chlorpromazine was administered.[33] Determining the incidence of dyskinesias following use of a specific drug is virtually impossible because most patients have received multiple drugs by the time the abnormal movement is recognized. When it occurs following the changeover from one antipsychotic drug to another, orofacial dyskinesia is more likely related to the discontinued drug than to the new drug which the patient was actually receiving when the dyskinesia was first recognized.

Irreversibility is a widely accepted characteristic of neuroleptic induced dyskinesias. More complete knowledge of the true incidence of remissions after drug termination or upon reduction of dose would be of great value both in understanding the basic pathophysiology as well as in management. Another pertinent question is whether duration of the dyskinesia is a factor in determining reversibility. If this is in fact shown to be the case, then early detection and appropriate management become critical, and suggest the need for periodic termination of neuroleptic treatment.[12] When remissions occur following discontinuation of the drug, they generally occur within a period of weeks to several months. However, six to seven months were required in one case.[17] It has been argued that irreversible oral dyskinesias following administration of phenothiazines were rare when cases with brain damage were excluded and the duration of follow-up exceeded six months.[34] However, brain damage is commonly found in patients with dyskinesia, even in reports which do not consider it as predisposing to dyskinesia.[18,19] There are relatively few studies providing sufficient detailed data to analyze the incidence of remissions, and some of these studies are summarized in Table 2. Of the 354 drug-induced cases followed for more than six months, in 293 or 82 percent dyskinesias continued to occur and in only 17 percent overall were there remissions. High remission rates of 41 percent[17] and 38 percent[35] have been reported, but follow-up duration was mentioned in only one of these series.[17] The apparent irreversibility may reflect the bias of studies made up predominantly of patients who have been in institutions for long periods and have been receiving long-term high dose treatment. Evaluation of an outpatient population who are presumably less incapacitated by psychosis, are younger, have a lower incidence of brain damage and are in a situation in which earlier recognition of dyskinesias might be possible might show different characteristics, especially with regard to incidence and reversibility. It is likely that cases of dyskinesias that have remitted on drug termination have gone unrecognized or unreported. At the present level of knowledge, most cases of orofacial dyskinesias should be considered as irreversible, even when drug use has been terminated.

TABLE 2.—*Remission of Dyskinesia After Drug Termination*

Source	*Total Number*	*Dyskinesias Remitted*		*Dyskinesias Persistent Follow-up Period*	
		Number	*Percent*	*Less Than Six Months*	*More Than Six Months*
Uhrbrand (1960)[17] ...	17	7	41	2	8
Hunter (1964)[16]	13	0	0	0	13
Degwitz (1969)[31]	273	52/52*	19/19*	0	169†
Edwards (1970)[15] ...	19	1*	5	0	18‡
Crane (1971)[36]	27	1§	3	0	26§
Hershon (1972)[37] ...	23	0	0	23	0
Klawans (1974)[23] ...	7¶	0	0	0	7

*Severity was reduced but dyskinesia was persistent.
†Includes 43 cases in whom severity was increased.
‡Includes five cases which worsened without administration of phenothiazines.
§Net result is shown; actual results include three who improved and two in whom orofacial dyskinesia developed when phenothiazines were not given.
¶Nonpsychotic phenothiazine induced cases.

A possible role of dental malocclusion has been considered in several papers. In one report, the dyskinesia of five patients with nonphenothiazine-related orofacial dyskinesia responded favorably to prosthetic dental therapy to correct the malocclusions.[38] A tendency to relapse when dentures were removed for long periods was commented upon and the authors suggested disruption of dental proprioception as a factor in the genesis of orofacial dyskinesia.[38] The dental status was examined in 368 cases of drug-induced orofacial dyskinesia.[18] Of 207 edentulous patients, dyskinesias developed in 46 percent. By contrast, of 161 patients who either wore dentures or had at least four of their own teeth, dyskinesias developed in only 21 percent. The authors concluded that patients with facial dyskinesias have difficulty in retaining dentures in their mouths, and that the edentulous state was a manifestation of oral dyskinesia rather than a significant cause in this disorder.[18] In several other series, the state of dentition was evaluated and not considered to be a significant factor.[13,15]

Spontaneous orofacial dyskinesias—that is, dyskinesias occurring in the absence of drug exposure and diseases known to be associated with dyskinesias—are considered to be rare, with a reported incidence of 1 to 2 percent.[19,20,39,40] However, several series report that in as many as 10 per cent[2] and 20 percent[18] of patients dyskinesias develop spontaneously. Most spontaneous dyskinesia cases occurred in patients residing in nursing homes or mental hospitals, and most of the patients were of advanced age.[2] As in the drug-induced variety, the spontaneous cases occur more often in women and in those with organic brain disease. Of 285 nonphenothiazine treated mental hospital patients, spontaneous dyskinesia was noted in 29 percent of the women and in 12 percent of the men.[18] Even when the cases of six women with a history of electroconvulsive therapy are eliminated, the incidence remains high at 24 percent. Clinical dementia was observed in half of the 20 men and in three quarters of the 36 women in this series; this was significantly higher than in drug-induced dyskinesia in women.[18] In another series, in more than a third of 40 patients with spontaneous dyskinesias there were diagnoses indicative of organic brain disease.[2] The most common underlying diagnosis, as in drug-induced dyskinesia, was either schizophrenia or affective psychosis.[2] Spontaneous orofacial dyskinesia presents a clinical picture indistinguishable from the drug-induced form.[31] The natural history, including spontaneous remissions, is largely unknown and no extensive series has been reported concerning this aspect. Two cases described in detail were refractory to multiple drug trials,[39] while a favorable response was obtained in most of 15 patients treated with tetrabenazine, pimozide or both.[41]

Basic Mechanisms

A biochemical explanation for orofacial dyskinesias has been advanced, based on several lines of evidence. The first is that neuroleptic drugs appear to act in part by blockade of central dopamine receptors.[42] This blockade has been postulated to then result in a state of "chemical denervation" of dopamine receptors in the striatum.[43] Some of these altered receptors are regarded as then developing "denervation hypersensitivity." Those neurons whose dopamine receptors have become hypersensitive may then respond abnormally to any dopamine to which they are exposed. However, direct proof of this hypothesis is still lacking. Besides receptor blockade, neuroleptics increase synthesis and block the reuptake of dopamine, thereby presenting sensitized receptors with additional amounts of dopamine. These effects would be expected to aggravate a state of receptor hypersensitivity.

A pharmacologic model of two types of dopamine receptors has been formulated.[43] One type of receptor is inhibited by dopamine and is associated with larger striatal neurons. This type is responsible for the rigidity of Huntington's chorea or drug-induced parkinsonism. The other type of receptor is facilitated by dopamine and is associated with smaller striatal neurons. This type is responsible for the chorea of Huntington's chorea and for orofacial dyskinesia. Furthermore, this latter type is blocked by doses of haloperidol and phenothiazines that do not affect the dopamine inhibited receptors. This model would be consistent with the observation that neuroleptic-induced dyskinesias may appear for the first time after reduction of the drug dose, and this is explained as reduced blockade of dopamine facilitated receptors.[43]

Recently, it has become possible to characterize dopamine receptors using dopamine and haloperidol labeled radioactively with tritium.[44] Findings in these studies indicate the presence of two types of dopamine receptors: one which is an agonist and binds dopamine and the other which

is an antagonist and exhibits greater affinity for haloperidol. Affinity for the antagonistic binding site was shown by phenothiazines in a rank order similar to their antipsychotic potency. In these studies, fluphenazine and haloperidol had 8 times the potency of chlorpromazine, 52 times the potency of promazine and 200 times the potency of promethazine. Application of these techniques to laboratory models of dyskinesia and to human cases may in the future permit more precise characterization of dopamine receptors and either support or invalidate the dopamine receptor hypothesis.

Certain other phenothiazine drugs are more potent dopamine receptor antagonists than others and this property has been linked to similarity of the molecular conformation to that of dopamine.[45] According to this hypothesis, substitutions on the basic phenothiazine nucleus will determine dopamine receptor blockade activity. Figure 1 indicates that basic phenothiazine nucleus with possible points of substitution indicated as R1 and R2. Halogen substitution at R1 such as in chlorpromazine, fluphenazine or trifluoperazine and substitution at R2 with a piperazine side chain such as fluphenazine or trifluoperazine is associated with high degrees of dopamine receptor blockade and with antipsychotic potency.[45]

Dopaminergic activity altered by neuroleptics may result in dyskinesia upon exposure to another drug. A guinea pig model for dyskinesia showed that stereotyped oral behavior analogous to human orofacial dyskinesia results when chlorpromazine pretreatment for several weeks is followed by omission of drug for one week and then by administration of amphetamine in low doses.[46] In mice, the period of dopaminergic supersensitivity in this paradigm appeared to be brief (observed at two but not nine days) and striatal adenyl cyclase activity was not altered.[47] In monkeys regularly treated with methadone (which is known to block dopamine receptors) and then maintained drug-free for at least two months, conspicuous oral dyskinesias developed in response to low doses of methamphetamine.[48] The authors suggested that the oral dyskinesias resulted from amphetamine-induced stimulation of striatal dopamine receptors made supersensitive by long-term methadone administration. Furthermore, they suggest that human patients maintained on methadone might exhibit hypersensitivity to amphetamine.

Another fundamental aspect of orofacial dyskinesia is that cholinergic and dopaminergic activity are in a state of balance. Certain observed effects suggest that cholingeric hypofunction, besides dopamine receptor hypersensitivity, is partly responsible for dyskinesias. Anticholinergic agents, given to reduce parkinsonism, have been reported to increase the incidence of drug-induced dyskinesias[3,43] and may increase the severity and lower the threshold for appearance.[43] Administration of scopolamine, an anticholinergic agent, worsened voluntary tongue activity, limb chorea and drawing ability in patients with tardive dyskinesias.[49] The opposite effects were observed after the administration of physostigmine, a centrally active cholinergic agent.[49] Similar effects of physostigmine and scopolamine were reported on the orofacial movements of patients with tardive dyskinesia.[50] Reversible orofacial dyskinesias appeared for the first time in six patients treated with anticholinergic agents.[51] Because of these deleterious effects on orofacial dyskinesias, it has been recommended that anticholinergic therapy be avoided as a routine addition to the use of neuroleptics.[43]

Reports of a relationship between extrapyramidal side effects and binding to the cholinergic muscarinic receptor in the brain is additional evidence of cholinergic involvement in orofacial dyskinesia.[52,53] According to this hypothesis, a high incidence of extrapyramidal side effects, including dyskinesia, result from low affinity of a neuroleptic drug for muscarinic receptor binding sites. Conversely, a low incidence of extrapyramidal side effects results from high affinity of a drug for muscarinic binding sites. Furthermore, this model provides a system whereby drugs may be screened for extrapyramidal side effects.[52] Therefore, it is theoretically possible to develop the "ideal" neuroleptic drug which combines potent antischizophrenic activity based on high dopamine receptor blockade and minimal extrapyramidal side effects related to high affinity for muscarinic receptors.

Clinical Therapy

Attempts to treat tardive dyskinesia have been disappointing and largely unsuccessful. At times, initial optimism following a preliminary report of success with a particular drug has been replaced by skepticism when subsequent reports indicate therapeutic failure. In this section, the various pharmacotherapeutic approaches to the treatment of tardive dyskinesias will be reviewed, primarily as to the effects on dopamine at central nervous system synapses.

Dopamine-depleting drugs

Reduction of dopamine should be beneficial, if receptor hypersensitivity to dopamine is a valid model. Reserpine, which depletes catecholamines from intraneuronal storage sites, has been evaluated in several series. Of 16 patients who received 1 mg per day of reserpine along with a neuroleptic, three had improved after one month and two more improved after more prolonged therapy.[54] Of another 16 patients treated with reserpine alone after the neuroleptic was discontinued, seven had improved after one month.[54] Neither withdrawal of the antipsychotic medication nor reserpine-induced rigidity was considered responsible for the improvement. Higher doses of reserpine (from 3 to 5 mg per day) were successful in five patients when lower doses were not effective.[55,56] Once the dyskinesia was controlled, the doses of reserpine were gradually reduced without recurrence of the dyskinesia.[56]

Tetrabenazine, like reserpine, prevents catecholamine storage, but is more rapid in onset and offset and has less hypotensive effect. Beneficial effects on the orofacial dyskinesia of three schizophrenic patients was observed within several days with administration of 75 mg per day of tetrabenazine, but 150 to 300 mg per day were required in a demented patient.[57] Rapid benefit within 24 hours was reported in a dyskinetic patient who received 200 mg of tetrabenazine.[58] In another patient, in whom there were acute dystonia, limb dyskinesia and akathisia after a single injection of fluphenazine, there was prompt response to administration of 150 mg of tetrabenazine.[58] Of six patients treated with 50 to 100 mg of tetrabenazine daily for one week, dyskinesia was abolished temporarily in three patients, but recurred shortly after administration of tetrabenazine was stopped.[59] At dosages up to 150 mg per day of tetrabenazine for six weeks, in 58 percent of 24 dyskinetic patients there was an improvement of 50 percent or more; the abnormal movements were totally suppressed in eight of these patients.[60] However, dyskinesia returned following the discontinuation of treatment with tetrabenazine.[60] Similar results were obtained when the treatment period was extended to 18 weeks, with alleviation of dyskinesia in two of six patients.[61] No further suppression of dyskinesia was achieved despite the longer treatment period or higher doses of up to 200 mg per day.[61]

Remarkable benefit has been reported with the use of tetrabenazine or pimozide (a dopamine receptor blocking agent), or both, in the treatment of 15 patients with spontaneous orofacial dyskinesia.[41] At a dose of 40 to 150 mg per day of tetrabenazine (median dose 75 mg) for 3 to 36 months, dyskinesia disappeared in four and improved in five other patients treated with this drug alone. When 2 to 3 mg per day of pimozide was combined with tetrabenazine, dyskinesia disappeared in all eight patients treated with the combination. Of particular interest is the rarity of recurrence when both drugs were administered together.

Lithium carbonate is widely used for the treatment of acute mania, and is regarded to act by reduction of dopamine at central synapses. One explanation for this effect was enhancement of monoamine oxidation, as suggested by reduced o-methylated and increased deaminated metabolites.[62] In a single patient in one early report[63] and in all six patients in another report, there was benefit from therapeutic doses of lithium.[64] Further studies appear warranted by these favorable reports.

Alpha methyl dopa has been reported to benefit some patients with tardive dyskinesia. There was improvement in two of three patients after treatment with 750 mg per day for one month.[54] By contrast, administration of 500 to 1,000 mg per day for six weeks failed to achieve benefit in any of nine patients with tardive dyskinesia.[65] This drug has two principal effects, namely inhibition of the enzyme dopa decarboxylase resulting in decreased dopamine formation and as a false neurotransmitter that has less "dopaminergic effect" than endogenous dopamine.[66] This dual action suggests this to be a potentially useful agent, but present data are not encouraging.

Alpha-methyl para tyrosine reduces dopamine concentrations by inhibition of the catecholamine synthesizing enzyme tyrosine hydroxylase. Treatment of eight dyskinetic patients with 3 grams per day for three days notably benefited six patients, with less definite reduction in one additional patient.[50]

Dopamine-augmenting drugs

Monoamine oxidase inhibitors increase the amount of dopamine available to synapses and if anything would be expected to worsen dyskinesia. Surprisingly, isocarboxazide, a monoamine oxidase inhibitor, when combined with chlorproma-

zine was effective in seven of eight patients with oral dyskinesia treated with this combination.[67]

Amantadine has clinical efficacy in the treatment of parkinsonism, and has some dopaminergic action, although preclinical studies have failed to clarify its specific effects.[68] Treatment of tardive dyskinesia with amantadine has been unrewarding as indicated by reports of failure in a combined total of 44 patients.[69-72] Earlier reports of benefit have been criticized as incorrect diagnosis[73] or retracted by the authors after conducting more extensive double blind studies.[74]

Dopamine-blocking drugs

It would appear logical to use drugs that block dopamine receptors to treat a condition that is modeled on hypersensitivity of these receptors. Available and potent receptor blockers include the phenothiazines and butyrophenones, which are also the major dyskinesia-producing agents. As a consequence, a paradoxical situation is encountered in which an antipsychotic drug might be used to control manifestations caused by that same or related drug. It has been observed clinically that increasing the dosage of the same neuroleptic drug the patient already had been receiving may improve orofacial dyskinesia.[75,76] Caution has been suggested in this approach, since a vicious cycle may be initiated of increasingly higher doses being required for dyskinesia suppression.[76]

Of the phenothiazines, thiopropazate in particular has been reported to benefit dyskinetic patients.[77-82] Pronounced reduction or complete disappearance of dyskinesia was reported in four

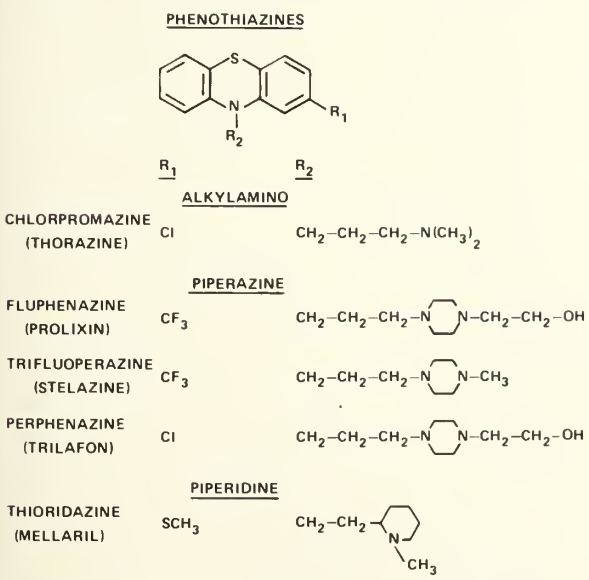

Figure 1.—Structures of phenothiazines and substituents.

of nine patients treated with 40 to 80 mg per day for four weeks.[81] It has been suggested that perphenazine is the active compound resulting from metabolism of thiopropazate, and perphenazine in a daily dose of 24 mg was effective in 14 dyskinetic patients.[81] Both perphenazine and thiopropazate contain the piperazine side chain (see Figure 1) and have potent dopamine and cholinergic receptor blocking action.[44,45,52,53] It has been suggested that the most potent dyskinesia-producing phenothiazines are also the most efficacious in suppressing dyskinesias.[82] Recent studies support a biochemical basis for this correlation.[44,45,52,53]

Haloperidol, a butyrophenone agent, is one of the most potent dopamine receptor antagonists[44] and is similar to the phenothiazines in that it has both dyskinesia producing[83] and dyskinesia alleviating action.[82] In six of 16 patients, orofacial dyskinesias were completely relieved by 8 to 16 mg per day of haloperidol given for four weeks.[82] In most of the patients in whom there was response to therapy with haloperidol, there had been favorable response to tetrabenazine administration in an earlier trial.[82] However, when haloperidol was given for 18 weeks, the initial alleviation of dyskinesias in five of seven patients was progressively lost, despite a doubling of dose.[61] Consequently, the clinical benefit from haloperidol may be of limited duration. As with phenothiazines, a cycle of increasing dosage may be necessary.

Pimozide, a diphenylbutylpiperidine, has relatively specific blocking activity against dopamine receptors.[84] In a double-blind study of 20 dyskinetic patients, pimozide produced significant benefit during a six-week trial.[84] The major side effect was the development of parkinsonism, which is consonant with the view that dyskinesia and parkinsonism represent opposite ends of a spectrum of excessive or insufficient dopaminergic activity.[84] In four patients with nondrug (spontaneous) oral dyskinesia, therapy with 2 to 3 mg per day of pimozide eliminated the dyskinesia.[41] When pimozide and tetrabenazine were combined, dyskinesia was totally suppressed in all eight patients receiving the combination. Furthermore, recurrence was rare when the two drugs were used in combination.

Cholinergic drugs

A balance of cholinergic and dopaminergic function is considered necessary for normal motor

activity.[49] Cholinergic hypofunction has been considered dyskinesia-inducing and administration of anticholinergic drugs may actually increase the incidence of orofacial dyskinesia.[3,43] It has been recommended that therapy with antiparkinsonian agents with anticholinergic action, such as trihexyphenidyl and benztropine, be avoided as a routine addition to treatment with antipsychotic drugs.[43]

Use of cholinomimetic agents, by contrast, may have beneficial effect in dyskinesias. Physostigmine is an anticholinesterase that crosses the blood brain barrier and increases the concentration of brain acetylcholine.[85] Intravenous injection of 1 mg of physostigmine lessened tongue movements in ten of 12 dyskinetic patients, and improved drawing ability in four of six patients tested.[49] However, these favorable results have not been found by others. After 1 mg of intravenously given physostigmine, only a slight reduction of dyskinesia was noted in four patients and no benefit in four others.[50] In another report of seven patients, no benefit or an increase in the dyskinesia was observed after the intravenous injection of 1 mg of physostigmine.[86]

Deanol, which is the dimethylaminoethanol salt of para acetamidobenzoic acid, is regarded as a choline precursor, and augments the cholinergic system.[87] Two brief reports indicated clear benefit in two patients receiving 600 mg per day[88] and in another receiving 1,600 mg per day.[89] However, subsequent reports indicate therapeutic failure despite doses of 1,600 mg per day in two patients[90] and in another series, despite treatment with 1,200 to 1,600 mg per day in 11 patients.[91] These results indicate a need for continued clinical trials to determine the role of deanol in the management of tardive dyskinesia.

In a patient with dyskinesia refractory to deanol (maximum of 2 grams per day for three weeks), there was response to 16 grams per day of choline chloride, after lower doses had been ineffective during the first week of treatment.[92] When administration of choline was stopped, dyskinesia returned.

Additional therapeutic agents

Pyridoxine (vitamin B_6) neutralizes the effects of L-dopa administration in patients with parkinsonism[93] including the side effect of dopa-induced dystonia.[94] Based on these observations, ten patients with neuroleptic-induced dyskinesia were treated with 300 mg of pyridoxine per day for 10 to 14 days, but with no benefit.[95]

Therapy with papaverine, a smooth-muscle relaxant used clinically as a cerebral vasodilator, improved orofacial dyskinesias in three patients when they were given 300 to 600 mg per day.[96]

Imbalance between serotonin and dopamine in the basal ganglia has been considered as contributing to orofacial dyskinesias.[97] In an attempt to increase brain serotonin, 6 grams per day of the serotonin precursor L-tryptophan was administered to four dyskinetic patients in a double-blind study.[97] This treatment temporarily suppressed dyskinesia in all the patients, but a tendency to relapse in a few days was observed.[97] This unsustained benefit was ascribed to temporary compensation of catecholamine predominance by enhancement of serotonin. Another serotonin precursor, 5 hydroxytryptophan, failed to benefit the one dyskinetic patient in whom it was tried.[98]

Clonazepam, an anticonvulsant of the benzodiazepine group, was reported to improve the dyskinesia in 42 patients treated with one to three mg per day.[99] This brief report offers the prospect of effective therapy for tardive dyskinesia, if these results are corroborated by other workers.

Therapeutic Approach and Summary

Present data on tardive dyskinesia suggest it is a symptom complex and not a single disease entity. Additional knowledge regarding the significance of such factors as duration of dyskinesia, the effect of continued administration of neuroleptics after recognition of dyskinesia and the optimal dose as well as duration of various therapeutic approaches may indicate these to be salient variables. It may be most appropriate to consider several biochemical mechanisms at the same time, with particular focus on the balance of cholinergic and dopaminergic activity.

When the results summarized in this review are considered, an appropriate approach might be to therapeutically challenge dyskinetic patients with different categories of rapidly acting agents.[50,101] This approach should include cholingeric agents (such as physostigmine), anticholinergic agents (such as benztropine), dopamine-depleting agents (such as tetrabenazine) and dopamine-blocking agents (such as pimozide and haloperidol). The responses to such a series of drugs may then provide a more rational basis to pursue specific therapeutic courses subsequently.

As discussed, administration of antipsychotic

medication should periodically be stopped and studies made for the presence of dyskinesia as well as to determine the need for continued treatment.[12,100] When dyskinesia is initially recognized, administration of the antipsychotic drug should be discontinued, or at least reduced to the minimum therapeutic level. Recent preclinical and clinical studies indicate that clozapine, a dibenzodiazepine, has potent antipsychotic activity and the lowest incidence of extrapyramidal side effects.[52,53,102] This drug may be especially suited for the patient in whom neuroleptics are required but in whom orofacial dyskinesia is present. Early recognition and, ultimately, prevention may be the only effective means of reducing the incidence of this disorder.

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Specialty Conference

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THEODORE FEIT, MD, PhD
THOMAS G. GOERGEN, MD
SYLVIA MICIK, MD
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Refer to: Stein M, Blayney D, Feit T, et al: Acute iron poisoning in children—University of California, San Diego, and University Hospital, San Diego (Specialty Conference). West J Med 125:289-297, Oct 1976

Acute Iron Poisoning in Children

WILLIAM L. NYHAN, MD, PH D:* *The problem of acute iron poisoning is a subtopic of the general problem of poisoning in childhood. We have asked Dr. Sylvia Micik to begin the discussion of this problem.*

SYLVIA MICIK, MD:† Since its inception three years ago, the San Diego Poison Information Center has had a remarkable history of success. The center has two major roles. The first is to provide to the public immediate access to information and treatment in the event of a poisoning. The second is to provide professional information and medical consultation for physicians in the community treating poisonings. In its first role, the center has received national recognition for its effectiveness. This center is currently receiving more calls per unit of population than any other in the United States. Of more than 20,000 calls per year that the center receives, about 85 percent come from the public. Of those calls that reflect actual poisonings, 88 percent are managed over the telephone by Poison Center staff. This capability provides crisis intervention and optimal utilization of emergency medical resources, and acts to prevent morbidity by prompt treatment and early recognition of those poisonings requiring further therapy. This system provides considerable cost savings to the community. In a selected sample of six San Diego hospitals with a pediatric service, there was a 40 percent decrease in poisoning admissions in children under 10 years of age since the opening of the Poison Information Center. In assisting health professionals in the treatment of poisonings, the Poison Information Center directs patients to appropriate community facilities and notifies emergency room staff of their arrival along with the necessary information for evaluation of toxicity and treatment. Consultation is provided to physicians treating poisoned patients. The Poison Center also coordinates transfer of patients to University Hospital when indicated.

Follow-up services, public education, prevention and data gathering and evaluation are all part of this system of care for poisoned patients.

DR. NYHAN: *We shall begin our consideration of iron poisoning with the presentation of a patient by Dr. Theodore Feit.*

THEODORE FEIT, MD, PH D:‡ Our patient was a 13-month-old white boy in good health until the day of admission when he ingested approximately 5 grams of elemental iron in the form of ferrous sulfate. His mother found him sitting next to the empty container and there was one pill lying on

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the floor. Previously there had been approximately 80 of the 300 mg ferrous sulfate tablets in the container. The child did not appear ill. The mother took him to a baby-sitter and went to work for the evening. The baby-sitter realized the gravity of the situation, called the Poison Information Center and was instructed to give syrup of ipecac, which was given an hour after ingestion. This resulted in a moderate emesis of greenish chalky material. She took the child immediately to a community hospital where he was again treated with syrup of ipecac. He was given sodium bicarbonate by mouth and referred to University Hospital where he arrived three hours after the ingestion.

On examination, the child was seen to be pale and semicomatose. Temperature was 96.4°F (35.8°), pulse 130 beats per minute and respirations 40 per minute. Blood pressure was normal. Skin texture was dry and doughy. The pupils were constricted. The patient had no spontaneous movement. His mental state fluctuated from almost awake and crying to obtunded with reaction only to deep pain. On roentgenograms of the abdomen, radiopaque pellets in the stomach and intestine were seen. The serum concentration of iron was 942 μg per 100 ml. (normal 60 to 150 μg per 100 ml.). Studies of arterial blood showed pH, 7.21; Po_2, 147 mm of mercury; Pco_2, 30 mm of mercury, and a base excess of minus 15. The following values were found: sodium, 137; potassium, 3.7; chloride, 108, and bicarbonate 14 mEq per liter. Hematocrit was 41 percent and the leukocyte count was 20,300 per cu mm with a normal differential. The child was given syrup of ipecac again with emesis of only a small amount of greenish material. The stomach was lavaged with 150 ml of 5 percent sodium bicarbonate in normal saline. He was then given 1 gram of deferoxamine intramuscularly. Two peripheral intravenous lines were placed in one of which Ringer's lactate was infused and in the other, whole blood. The child was given 1 gram of deferoxamine by intravenous push. His condition appeared more like shock and 100 ml of whole blood and 5 grams of salt-poor albumin were given. He had not voided for five hours after admission. He was then given 10 mg of furosemide (Lasix®) and a urine output of 100 ml per hour of reddish-orange urine was established which persisted throughout the next day.

The day following admission the child was alert and oriented. On repeat roentgenogram of the abdomen, radiopaque pellets were seen and he was given an enema. One gram of deferoxamine was given in continuous intravenous infusion over 24 hours. Urine output remained good. Hematocrit and vital signs remained stable. The serum iron level was 315 μg per 100 ml. Two days after admission the urine had turned clear yellow. The serum iron level was 113 μg per 100 ml. He remained well. He was given another gram of deferoxamine intravenously over 24 hours. The serum iron decreased to 42 μg per 100 ml. on the next day and the child was discharged.

DR. NYHAN: *We shall turn now to Dr. Thomas Goergen who will discuss the x-ray studies.*

THOMAS G. GOERGEN, MD:* The initial abdominal film made at University Hospital approximately four or five hours after the ingestion showed a collection of amorphous material over the left upper quadrant, probably in the stomach. Several tablets could be seen in the gastrointestinal tract, either in the small bowel or in the colon. A second abdominal film 12 hours later showed several remaining tablets overlying the distribution of the left colon and sigmoid.

A few years ago a member of the University of California, San Diego, Radiology Department radiographed more than 200 solid medications and found that 20 percent of them were moderately or faintly radiopaque.[1] All enteric-coated medications were at least moderately radiopaque and resisted disintegration in gastric juice for at least two hours. The reason the enteric-coated compounds are radiopaque is not clear. The atomic weight of the variety of materials used in coating would not seem to be sufficiently high to explain the degree of radiopacity. The mnemonic "CHIP"—for chloral hydrate, iron and phenothiazine—may help one remember some of the more commonly used radiopaque medications.

If one looks at the iron preparations as a group, almost all are highly radiopaque and can be seen on abdominal films until they reach a fine consistency. A positive postingestion radiograph, that is, the presence of radiopaque tablets or amorphous material, may be helpful in directing treatment. In this case, after the discovery of several tablets over the distribution of the colon on the second abdominal film, an enema was given. Tablets remaining in the stomach or small bowel may signal the need for additional

*Assistant Professor of Radiology.

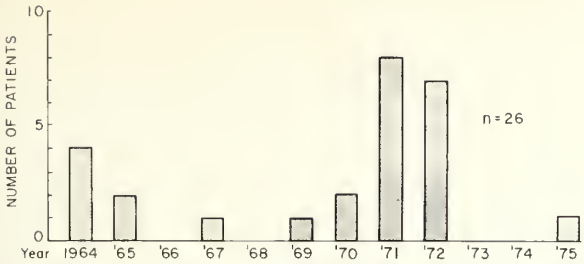

Figure 1.—Incidence of iron ingestion in patients treated at University Hospital, San Diego.

TABLE 1.—*Sources of Iron Ingested*

Ferrous sulfate ($FeSO_4$)	14
Ferrous fumarate	2
Ferrous sulfate and ascorbic acid (Vitron C®)	2
Geritol®	1
Fermet®	1
Ferrous gluconate (Fergon®)	1
Ferrous sulfate (Fer-in-Sol®)	1
Ferrous fumarate (Toleron®)	1
Chocks c̄ Iron®	1
Prenatal vitamins	1
"Vitamins"	1
	26

TABLE 2.—*Clinical Data on 26 Patients with Iron Ingestion*

Age of Patient (Months)	*Amount of Iron Ingested*		*Blood Concentration μg/100 ml*	*Clinical Manifestation*	*Treatment*
	mg	*mg/kg*			
18	900	..	..	V	EDTA
12	1,200	90	401	V	EDTA
16	2,400	230	..	D	EDTA
30	2,400	220	..	V	EDTA
24	1,400	103	134	VDL	..
42	3,000	270	83	..	..
13	820	82	..	L	..
48	585	47	790	VD	DEF
24	820	76	240	..	DEF
18	400	36	185	..	DEF
14	250	21	250	..	DEF
15	..	..	378	VL	DEF
36	225	16	388	VD	DEF
36	..	..	260	..	DEF
32	720	54	80	VD	DEF
36	7,670	700	9,000	VDLS	DEF
24	4,500	450	1,770	VLS	DEF
36	590	46	..	D	DEF
31	1,820	130	300	VD	..
30	1,080	90	365	..	DEF
25	..	..	275	V	DEF
11	1,200	140	600	VL	DEF
21	1,200	120	290	..	DEF
36	1,960	150	420	VD	DEF
22	..	..	330	VL	DEF
26 yrs	"suicidal gesture"		55	..	..

The amounts of iron ingested were generally estimates. Where no figure is given there was not enough information to permit an estimate. The clinical manifestations most frequently encountered have been designated by their first letters; vomiting (V), diarrhea (D), lethargy (L) and shock (S). Before 1969 some patients were treated with ethylene diaminetetraacetate (EDTA). More recently most patients have been treated with deferoxamine (DEF).

lavage or cathartics. A negative radiograph does not exclude disintegrated tablets remaining in the gastrointestinal tract.

DR. NYHAN: *Thank you, Dr. Goergen. We would like to turn now to Mr. Douglas Blayney.*

DOUGLAS BLAYNEY, BS:* During the course of treatment, our team became interested in examining the experience with previous cases of iron ingestion at University Hospital. I undertook a retrospective study of patients seen from January 1964 to September 1975. In that period there were 26 cases of iron ingestion.

Figure 1 depicts data on the incidence by year. It is not clear what factors are responsible for the unusually high number of patients seen in 1971 and 1972, or the paucity of patients seen since 1972. However, several records in the 1970 through 1972 period mention, as reason for referral to University Hospital, an unavailability of deferoxamine at the referring hospital.

Table 1 presents the list of iron sources in all 26 ingestions. Ferrous sulfate ($FeSO_4$) heads the list, as the source in more than 50 percent of the cases. Although "vitamins" and "prenatal vitamins" are listed separately, they probably also represent ferrous sulfate.

Table 2 summarizes the clinical information obtained from hospital records. The cases are listed in order of occurrence. The second column, which shows the amount of iron ingested, gives only the weight of elemental iron and not the amount of ferrous salt. The amount of iron ingested, as determined by the history, did not always correspond with the initial serum iron level, which was usually determined within four hours of ingestion. Major symptoms manifested were vomiting, diarrhea, lethargy and shock. Some children remained asymptomatic, usually because a responsible adult discovered the ingestion and promptly induced emesis. In patients with symptoms, vomiting was almost universal. In only two did shock develop. In 1964 ethylene diaminetetraacetate (EDTA) therapy was used, then discontinued when deferoxamine subsequently became available.

In two patients treated in 1971 there were very high serum iron levels: a 24-month-old infant in whom initial serum iron concentration was 1,770 μg per 100 ml spent two days in hospital and was discharged without residual symptoms; a 36-month-old infant in whom initial serum con-

*Medical Student.

centration was 9,000 μg per 100 ml was in hospital for two weeks and surgical operation on the abdomen was required for intestinal obstruction two months later. The one adult in the series was a 26-year-old woman whose ingestion was interpreted as a suicidal gesture.

Follow-up plans for the patients were determined by reference to either progress notes or discharge orders. Of the 26 patients, six were referred to their private or referring physicians. For ten patients, University Hospital clinic appointments were made. Three of these appointments were kept. For the remaining ten patients no provision for follow-up was listed or a "return prn" statement was made. Three of these ten patients subsequently presented with an unrelated complaint, and at that time no sequelae of their iron ingestion were seen.

In summary, of 26 patients treated for iron ingestion, nearly all (25 of 26) were 4 years of age or under. Remarkably, no cases of fatal ingestion of iron were among those seen.

QUESTION: *It is surprising that not one fatality occurred. Are fatal cases handled differently by the medical records department?*

MR. BLAYNEY: No, the medical record librarian assured me that case records of fatalities are not separately classified.

LAUREN PLUMER, MD:* As I remember, in 1971 a child who had ingested iron was dead upon arrival in the emergency room.

QUESTION: *Were there other patients with later complications or stricture or other gastrointestinal problems?*

MR. BLAYNEY: Not that could be determined from the medical records.

QUESTION: *Was there a mention of previous or subsequent proisoning in any of these children?*

MR. BLAYNEY: One child had a history of previous secobarbital (Seconal®) ingestion.

CHARLES INMAN, MD:† *Were child-proof containers involved in any of these cases?*

MR. BLAYNEY: That was one of the things I looked for, but none of the records mentioned child-proof containers. The paucity of cases since 1972 may reflect the recent utilization of these containers.

DR. NYHAN: *Thank you very much. We shall now turn to Dr. Martin Stein for discussion.*

MARTIN STEIN, MD:‡ The 13-month-old infant presented by Dr. Feit represents a clinical problem that has received considerable attention in the pediatric literature over the past 20 years. Nevertheless, the general public, as this patient presentation illustrated, has little understanding of the seriousness of acute iron poisoning in children. People tend to equate iron pills with vitamins and ascribe innocence to both. Acute iron poisoning is neither benign nor innocent.

Iron is one of the most abundant of metals. Its biologic importance is apparent in its role in hemoglobin and in the Krebs cycle. Of approximately 24 enzymes involved in aerobic glycolysis, 11 contain iron as an active part of the molecule or require iron as a cofactor. Iron has been used for the treatment of anemia for centuries. Poisoning by iron can be related to the status of iron therapy in history. In the middle 19th century, there were many reports of accidental poisoning from iron salts. This was a period when iron preparations were frequently prescribed by physicians. In the late 19th century, several distinguished European physicians voiced strong opposition to the use of medicinal iron in treating anemia. In retrospect their analysis was based on less than adequate doses of iron. However, the therapeutic use of iron decreased and, significantly, so did the incidence of acute iron poisoning. In the second and third decades of this century, the therapeutic benefit of iron salts was rediscovered, and, with its rediscovery, a case of accidental iron intoxication was reported in 1934. A clinical-pathological report of iron poisoned children was published in 1942.[2]

The National Clearinghouse for Poison Information Centers has estimated that 2,000 acute iron poisonings occur in the United States annually in children. At the San Diego Poison Information Center, there has been an average of 25 phone calls for iron poisoning each year since 1973. From 1964 to the present, 25 children were admitted to University Hospital with acute iron ingestion. In national statistics, iron ranked sixth among medicines causing admission to hospital due to poisoning in children under five. Before

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†Doctor in audience.
‡Assistant Professor of Pediatrics.

the introduction of specific chelation therapy, the mortality in children admitted to hospital with acute poisoning from iron ingestion was 50 percent.[3] Today it is considerably less.

Before discussing the toxicology of iron I would like to look at the problem of poisoning in children from a developmental point of view. We perceive the child as a dynamic human being who develops motor, language and social-behavior skills in a predictable time related manner. Although each child achieves these developmental milestones at his or her own rate, the progression of events is predictable, not only in time but also in order. For an infant to be at risk for most forms of childhood poisoning, two crucial developmental stages must have been reached. One is the development of a delicate pincer grasp, and the other is the ability to move to a poison. A child at birth has a reflex form of grasping in response to palmar stimulation and gradually develops reaching out for objects with simple purposeful movements by 6 to 7 months of age. At that time there is a clawing type of grasping movement. At 9 or 10 months a very delicate pincer grasp develops in which the first and second digits oppose each other. The pincer grasp is important not only in overall development, but it is a necessary condition for the picking up of small pills. The same kind of progression can be seen in the postural control of locomotion. Around the first birthday most children begin to be able to get to poisons. With the achievement of these voluntary movements and what might be termed a universal oral inquisitiveness, the infant approaching the first birthday is at risk for poisoning. The patient presented this morning was 13 months old.

From an epidemiological point of view, there are three primary factors in any childhood poisoning: the development of the child, the child's environment and the poisonous substance itself. The environment may provide the groundwork for an accidental ingestion. High-risk environmental factors include keeping poisons in easy access of a child and a disorganized family environment, especially at times of acute stress. Other high-risk environmental factors include poor housing, overcrowding, and deprived social and economic settings.

The poisonous substance plays an essential role. As in the case of acute iron intoxication, parents may be unaware of its hazards in large doses. Sugarcoated, brightly colored pills provide an attraction to the ever-exploring inquisitive child. Lack of effective safety packaging or placing a poisonous substance in an easy access container is a frequent antecedent to childhood poisoning. In a case of iron poisoning, it is not unusual to discover that the mother of the poisoned child is pregnant and that the iron was prescribed as a part of routine prenatal care.

The *Physicians' Desk Reference* lists 106 iron preparations.[4] Most of these are composed of three salts of ferrous iron: sulfate, fumarate and gluconate. It is important to appreciate that the amount of elemental iron in a particular salt preparation is variable. The elemental iron content of ferrous sulfate is 20 percent of its salt content; ferrous fumarate, 33 percent, and ferrous gluconate, 12 percent. Ferrous sulfate accounts for most acute poisonings in children. In general, most adult tablets contain 60 to 65 mg of elemental iron. Children's tablets contain 10 to 18 mg of elemental iron. The availability of many preparations over the counter and without safety cap mechanisms is a problem. I took photographs at several San Diego pharmacies to show the considerable over-the-counter availability of iron preparations. One of the real problems in the genesis of poisoning is the similarity of the appearance of many iron tablets to that of the popular M & M® candies.

The estimation of the number of tablets ingested in a particular case is no more reliable than in any other form of poisoning. Nevertheless, it is useful to inquire about the number of tablets present before and after an ingestion. The amount of elemental iron can be calculated, and some estimation of the toxic potential can be made. The minimal toxic dose at which symptoms are likely to occur is 20 to 60 mg of elemental iron per kg of body weight. In a 15 kg child this means that as little as 1 gram of ferrous sulfate or three adult sized tablets may cause toxic symptoms. The average human lethal dose is not known, but most investigators quote a figure of 200 to 250 mg per kg of body weight of elemental iron. For a 2-year-old child of average size this may mean an ingestion of 4 grams of elemental iron, the amount of iron present in 60 ferrous sulfate tablets (65 mg of elemental iron per tablet).[5] This is less than the estimated amount of iron consumed by the infant presented in the case today.

The clinical features of acute iron poisoning have been described. Four distinct phases have been delineated. In the first phase, nausea and vomiting begin usually within an hour after the

ingestion of a large dose. Hematemesis, melena and abdominal pain occur frequently. Peripheral vascular collapse follows soon. The patient seen at this time may be in shock and may have a gray cyanosis, lethargy, restlessness, tachypnea and tachycardia. Coma may develop rapidly and death may occur early. Approximately a fourth of deaths from iron poisoning occur within the first six hours. With vigorous supportive therapy the child's clinical status may improve in the second or quiescent phase. Alternating periods of lethargy may develop, but the blood pressure remains stable. Complete recovery may follow or this early improvement may be deceptive, and phase three may ensue.

The critical third phase begins 12 to 48 hours after acute ingestion. Profound shock may develop, associated with cyanosis, metabolic acidosis, lethargy, leukocytosis and fever. Hematemesis and melena continue as manifestations of a severe gastroenteritis. At this time, hepatic injury becomes apparent with the development of hyperbilirubinemia and elevated liver enzymes. In those children surviving phase three, recovery is rapid after two or three days. Late sequelae are rare. Pyloric stenosis secondary to scarring, as well as gastric fibrosis and stricture formation have been documented six weeks after the acute phase.

There have been several reported autopsies in children and three in adults after death from acute iron poisoning. Pathologic findings have been shown in experimental animal models.[6] The gastrointestinal tract is strikingly altered as a result of the corrosive action of ingested inorganic iron. The contents may be dark brown and frankly bloody. There is usually extensive erosion and ulceration of the stomach and small intestine. Microscopically, there is coagulative mucosal necrosis associated with hemorrhage and vascular congestion. There is a lack of correlation between the severity of intestinal damage and death. This suggests that the hemorrhagic gastroenteritis is not the major cause for the shock that is present in all fatal cases.

Hepatic dysfunction is found in the more severe cases of acute iron ingestion. This is apparent in the jaundice, direct hyperbilirubinemia and transaminase elevations. Histologic alterations in the liver in fatal cases in humans and in experimental animal studies are variable. In some fatal cases in humans no histologic changes in the liver have been seen, while in others there have been a variety of alterations including cloudy swelling, portal iron deposition, fatty metamorphosis and massive necrosis.

Other pathologic changes found at autopsy include fatty degeneration of the myocardium and masses of granular iron-containing material in the capsular space and in the lumen of the tubules of the kidney. Renal tubular degeneration has been reported rarely.

Experimental iron poisoning in animal models using rabbits has shown these to be pronounced hepatocellular degeneration. On examination of these rabbit livers by electron microscopy, mitochondrial injury of hepatocytes has been found. Results of histochemical analysis have shown alterations in a number of hepatic cell oxidative enzymes which provides an experimental model that may explain the lactic and citric acidemia seen in acute iron poisoning.

The occurrence of a coagulation defect following acute iron poisoning was initially suspected 15 years ago when an astute pediatrician reported excessive bleeding from needle puncture sites in a child who eventually died from acute ingestion.

Metabolic acidosis occurs in acute iron poisoning. The frequency of its occurrence is not well documented but it was present in the case presented. Three factors may contribute to metabolic acidosis: the release of hydrogen iron from the conversion of iron from the ferrous to the ferric form, the accumulation of lactic acid from anaerobic metabolism and the effect of iron as an inhibitor of enzymes of the Krebs cycle.

Shock is a cardinal feature of acute iron poisoning. In all reported cases of fatal iron poisoning, death has been preceded by shock. The presence of shock is not always correlated well with the degree of elevation of the iron serum. Shock may occur in the first six hours and again 24 to 48 hours after ingestion. It is uncertain whether the shock is initiated by a direct action of absorbed iron on the blood vessels or through the release into the circulation of excessive quantities of ferritin, a potent vasodepressant. However, increased ferritin was not found in the only dog with lethal iron poisoning in which it was measured and there are no data on ferritin levels in human iron poisoning. Another possible clue to the cause of shock was the discovery in animal studies of elevated plasma levels of two vasoactive substances, serotonin and histamine.

Hemodynamic considerations in the two animal studies showed six consistent features: decreased cardiac output, increased peripheral vascular re-

sistance, decreased plasma volume, hemoconcentration, decreased total blood volume and decreased blood pressure. This information is consistent with the development of postarteriolar dilation and subsequent venous pooling. This has been thought to be the primary physiologic event in the shock found in iron poisoning. An important clinical point to be derived from these animal studies is that the progressive decrease in blood pressure is not as rapid as the decrease in cardiac output. Thus, blood pressure cannot be relied upon as a totally accurate index of the severity of the hemodynamic alteration. Unfortunately, it is all that we have under clinical circumstances.

The clinical management of an acutely poisoned child is directed toward the pathophysiologic changes of iron intoxication. Removal of the iron is a primary concern. This can be promoted by inducing emesis, either by oral administration of syrup of ipecac or parenteral administration of apomorphine. The presence of syrup of ipecac in the home saves precious time in such an emergency. By emptying the gastric contents early, a potentially severe iron ingestion may be changed to a mild ingestion. The advantages of inducing emesis at home are apparent when the time saved in reaching an emergency facility is considered. Emesis induced by syrup of ipecac occurs in at least 90 percent of cases. It occurs in somewhat less than 20 minutes on the average.[7] Improved public education about poisoning and the availability of syrup of ipecac could be seen in the patient presented this morning and may well have altered the clinical course.

Experimental models have shown that induced emesis empties approximately 30 percent of the stomach contents,[8] an amount not exceeded by gastric lavage using the usual sized nasogastric tube. In the case presented there were two episodes of ipecac induced vomiting and gastric lavage was carried out. Following these procedures, a film of the abdomen showed tablet-shaped, radiopaque material in both the stomach and small intestine. Gastric lavage should be done using a large bore tube whether or not the child has vomited. When carrying out gastric lavage for poisoning the largest tube that can be passed with ease should be used.

Lavage fluids appropriate for iron ingestion include a 1:4 solution of a Fleet® Brand enema, which contains disodium phosphate. This will combine with ingested iron to form ferrous phosphate which is poorly absorbed. In a similar fashion, a 5 percent solution of sodium bicarbonate will form ferrous carbonate which is also poorly absorbed. After lavage an equal amount of solution should be left in the stomach. In addition, 5 to 10 grams of deferoxamine should be introduced into the stomach via the lavage tube. Deferoxamine has specific chelating properties for iron and will form a complex which is then excreted in the stool. Gastrointestinal absorption of the iron-deferoxamine complex is no greater than 15 percent, even in the presence of a damaged intestinal mucosa. The relatively small amount of chelated iron that is absorbed in this manner appears not to disassociate within the circulatory system and is excreted in the urine. This point is important to emphasize because the use of oral deferoxamine is sometimes withheld because of a concern about possible absorption of a deferoxamine-iron complex.

Parenteral chelation therapy with deferoxamine is an important, specific aspect in the management of acute iron poisoning. Its availability since the early 1960's decreased the mortality of severe iron poisoning. Deferoxamine (Desferal®) was isolated from the microorganism Streptomyces pilosus. It is a nearly specific chelating agent with an extremely high affinity for iron. Deferoxamine binds the iron of ferritin and hemosiderin while the iron of transferrin is removed minimally. The iron in cytochromes and hemoglobin is not accessible. Deferoxamine binds 8.5 mg of ferrous iron per 100 mg of chelate. The bound iron is nontoxic and excreted in urine. Iron alone is not excreted to any appreciable extent in urine but the iron-deferoxamine complex, called ferrioxamine, is readily excreted in urine.[9]

The side effects of parenteral administration of deferoxamine are minimal when used appropriately and cautiously. In early clinical trials, there were a number of reports of hypotension associated with the rapid intravenous administration of deferoxamine. When the drug was discontinued the blood pressure immediately returned to normal. Animal experiments have supported the observation that hypotension may be secondary to deferoxamine and ferrioxamine, the iron chelate. Hypotension is not seen where deferoxamine is given at a rate no greater than 15 mg per kg of body weight per hour intravenously or by the intramuscular route. Other side effects reported have included rashes and cataracts, but cataracts have been seen only after chronic use.

In 1965 Whitten and associates[10] reviewed the literature on clinical experience with iron poisoning. Most of the reports dealing with children were made before the availability of deferoxamine. Of the 26 children with iron ingestion who were neither in shock nor in coma, all survived. The presence of shock or coma precluded survival in patients not receiving therapy. Supportive therapy saved about half of such patients. Chelation therapy or exchange transfusion was associated with a 15 percent death rate, two of 14 patients with shock or coma. In 1966, Westlin[11] reported 272 cases of children with acute iron intoxication from several centers throughout the United States. All received deferoxamine. Of the 144 children without shock or coma, all survived. Of 28 children with shock or coma, three died—one of these, however, was not treated with deferoxamine until the third day after ingestion. The overall mortality rate from this large series was 1.7 percent.

Clinicians have attempted to correlate initial levels of serum iron with the degree of toxicity. There are limitations to this approach, especially the difficulty in obtaining serum iron values soon enough to influence therapy. It usually takes two or three hours and decisions must be made before getting the initial serum iron value. Nevertheless, when the serum iron level is over 350 μg per 100 ml, the serum transferrin binding capacity is exceeded and the patient may be considered poisoned.

The currently recommended use of deferoxamine in acute iron poisoning includes its use orally through a nasogastric tube. In a patient not in shock or severely intoxicated, the drug can be given safely by the intramuscular route in a dose of 1 to 2 grams. I would recommend 1 gram in most children, to be repeated every 3 to 12 hours depending on the clinical status, estimated amount of iron ingested, the serum iron level and the color of the urine in response to therapy. The presence of the chelated ferrioxamine in the urine imparts a vin rosé color to the urine. In a severely ill patient and any patient in cardiovascular collapse, deferoxamine should be given intravenously: a slow infusion at the rate no greater than 15 mg per kg of body weight per hour is recommended. It can be repeated after a gram is given every 4 to 12 hours again depending on the patient's clinical status and the color of the urine. Deferoxamine may be used as a diagnostic test of acute iron poisoning. The vin rosé color of the urine in response to deferoxamine would indicate the need for therapy.

In a severely iron poisoned child whose clinical condition is not significantly improved following the use of deferoxamine, the clinician must turn to other forms of therapy in order to decrease the iron load. Three modalities have potential use: peritoneal dialysis, hemodialysis and exchange transfusion. Although free iron is not dialyzable, the chelated deferoxamine complex can be removed by either peritoneal dialysis or hemodialysis. Perhaps the best clinical results, however, have been obtained with exchange transfusion. There is excellent experimental evidence from studies using animals that exchange transfusion is many times more effective than deferoxamine administration in removing iron from the body.[12] These methods are of particular importance in a child with renal shutdown.

A guide to when a child who is without symptoms but has ingested iron should be admitted to hospital might be to admit any child who has ingested 30 mg of elemental iron per kg of body weight. That amount is equivalent to half an adult ferrous sulfate tablet per kilogram of body weight. For a 2-year-old child, this would mean an ingestion of seven adult ferrous sulfate tablets. A 24-hour observation period to see if in this child any symptoms develop seems reasonable. In these children results of liver function tests should be evaluated following recovery. Symptoms that suggest gastrointestinal obstruction, which occurs secondary to gastric or pyloric scarring because of the corrosive effects of iron, should be evaluated by contrast studies of the upper intestinal tract.

No discussion of poisoning of children would be complete without a plea for prevention. Poisoning is usually preventable. Pediatricians, family physicians, nurse practitioners, public health nurses and office nurses all have the opportunity to prevent poisoning in high-risk infants and toddlers. Parents should be encouraged to keep all medicines and household chemicals away from children. The chance of having a second poisoning episode is 50 percent in a child who has had an initial poisoning. In these families more than the usual discussion about prevention is needed.

Safety capping of all medicines should be encouraged. Parents should be counseled not to consume their own medications within the view of an infant or toddler. Parental behavior is often mimicked by a child. A pregnant woman with a

small child in the house should be made particularly aware of the hazard of iron ingestion. Preventive pediatric care can be practiced optimally when the parent is given a one ounce bottle of syrup of ipecac at the 10 to 12 month well child visit along with proper instructions for its use. Parents may refresh their information on the use of ipecac by calling their physician or a poison information center.

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Lymphedema After Mastectomy

DR. LEIS: Patients do get swollen arms after mastectomies. And let me emphasize that they also get swollen arms after just radiation therapy . . . You get about the same percentage of arm edema as you would if you did a radical mastectomy. The lymphatics are destroyed one way or another. You also get the same percentage of arm edema in doing a simple mastectomy and following it with radiation therapy as you do with a standard radical. We define significant arm edema as being over 3 cm in measurement in the forearm as compared to the other forearm. And we know that you can increase this chance of edema by having an obese patient . . .

DR. JONES: We do a number of things to avoid lymphedema. We try to avoid a skin slough by several means. We leave about 4 to 5 ml of fat on the skin. I think it's clear that, if you get the skin flaps too thin, you can get a slough; and, in the process of sloughing and healing, you'll get plugging of the remaining lymphatics and are more likely to get a permanent edema. We usually trim the edge of the skin flaps where we've been holding on with clamps of any kind. We avoid closing under tension . . . We don't pull the catheters before the fluid has quit draining. We avoid the cephalic vein in our dissection and that's why I think many surgeons leave part of the pectoralis major muscle so that we can avoid that cephalic vein—not for the vein so much as for the fact that, frequently, the only lymphatic coming from the arm in postradical mastectomy patients is the lymphatic that accompanies that vein . . . With any sign of edema, we put stockings on; Jobst stockings are preferred. We start exercise in about 7 to 9 days. We don't use postoperative irradiation unless clearly indicated, since, as Dr. Leis indicated, this definitely increases the risk of arm edema. We carefully instruct every patient on the care of the hand. We warn them that if an infection develops in their hand sometime postoperatively, they're apt to end up with a delayed edema because of plugging of the remaining lymphatics.

—HENRY P. LEIS, JR., MD, *New York City*
ROBERT F. JONES, MD, *Seattle*
Extracted from *Audio-Digest Surgery*, Vol. 22, No. 17, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Rhabdomyolysis—Medical Staff Conference, University of California, San Francisco. West J Med 125:298-304, Oct 1976

Rhabdomyolysis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Today we are going to present the case of a patient in whom rhabdomyolysis developed for which we have no clear-cut explanation. In our ignorance we assume that it was secondary to "a virus infection." Dr. Haughom will summarize the case presentation.*

Case Summary

DR. HAUGHOM:† This was the first admission to the University of California Medical Center for a 45-year-old mother of seven children. The patient had been transferred from Modesto for evaluation of severe swelling and tenderness of the legs and arms following an influenza-like syndrome. Approximately two weeks before admission, the patient reported that an influenza-like illness had developed in her children, associated with cough, symptoms of upper respiratory infection and weakness. They subsequently recovered, but then the patient herself noted the onset of similar symptoms one week before admission. She noted symptoms at that time of feeling weak, coughing with production of a small amount of white to brown sputum, a runny nose, sore throat, occasional temperature to 104°F and intermittent chills. Five days before admission she further noted the onset of low back pain and bilateral leg pains. Leg pain increased and her legs began to swell, for which she consulted her private physician.

An initial diagnosis of influenza-like syndrome was made and pain medications were prescribed. These failed to relieve the pain, and the swelling continued until she was unable to walk or stand on her legs. The patient was admitted to a local hospital where her legs were noted to be swollen and tender to a pronounced degree; her arms were somewhat less swollen. Significant laboratory data at that time showed a leukocyte count of 17,000 per cu mm with 80 percent neutrophils, a value for creatine phosphokinase (CPK) of 5,653 IU per liter and normal findings on analysis of urine. Treatment with glucocorticoid hormones was begun. The following day the urine was found to be dark red in color, but no red blood cells were seen in the sediment. The patient was then transferred to the University of California Medical Center so that further evaluation and treatment could be carried out.

In response to questions, the patient said that there had been no significant previous illness, and that she had noted no headaches, stiff neck, photophobia, difficulty in vision, shortness of breath, nausea, vomiting, diarrhea, dysuria, hematuria or arthralgia. There was no recent history of animal or insect bites, recent travel or medicine ingestion. She also said that there had been no recent chemical or toxin exposure. The remainder of the medi-

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†John Haughom, MD, Assistant Resident in Medicine.

ABBREVIATIONS USED IN TEXT
BUN = blood urea nitrogen
CPK = creatine phosphokinase
CPK-2 = CPK isozyme-2
CPK-3 = CPK isozyme-3
PAH = para-aminohippurate
SGOT = serum glutamic-oxaloacetic transaminase
TEM = tetraethylammonium

cal history and review of systems was noncontributory.

On physical examination, the patient was noted to be somewhat heavyset and in moderate distress because of pain in the legs. Blood pressure was 140/90 mm of mercury, pulse 110 beats and regular, temperature 98°F (36.7°C) rectally and respiratory rate was 20 per minute and regular. The skin was dry and cool to the touch, no rash was present and no adenopathy was detected. The neck was supple and there was no jugular venous distention noted. Examination of the chest showed a few dry bibasilar rales but the chest was otherwise clear. Findings on cardiovascular examination were remarkable only for grade II/VI systolic ejection murmur. The abdomen was soft, bowel sounds were normal and there were no masses, tenderness or hepatosplenomegaly. Results of rectal examination were within normal limits. A stool specimen was guaiac negative. Musculoskeletal examination showed no costovertebral angle tenderness and there was no sacral edema. The legs were notably swollen bilaterally; the skin was tense and very tender but no erythema was found. The feet were cool bilaterally from the ankles down with poor peripheral pulses. Both arms were also swollen and tender but less so than the legs. Neurological examination was within normal limits.

Laboratory data on admission included a hematocrit reading of 40.7 percent and leukocyte count of 27,500 per cu mm with 76 percent polymorphonuclear cells. A specimen of urine was seen to be burgundy in color; on analysis, pH was 6, there were no red cells in the sediment, and the specimen was strongly positive for myoglobin. Findings on x-ray films of the chest showed no abnormalities. On an electrocardiogram diffuse precordial T-wave inversion was seen. Studies of electrolytes gave the folowing values: serum sodium, 121; potassium, 5.2; chloride, 90, and carbon dioxide (CO_2), 22 mEq per liter; serum calcium was 7.1 mg per 100 ml on admission. CPK was greater than 14,000 IU per liter, with 48 percent CPK isozyme-3 (CPK-3) and 52 percent CPK isozyme-2 (CPK-2); aldolase was 210 milliunits (mU) per ml (normal: 2 to 9), and serum glutamic-oxaloacetic transaminase (SGOT) was 560 IU per liter (normal: 5 to 40).

It was felt at the time of admission that the patient was suffering from an acute viral myositis with associated rhabdomyolysis and myoglobinuria. An intravenous line was placed and hydration carried out vigorously with normal saline and sodium bicarbonate solution to alkalinize the urine. High doses of glucocorticosteroids were also administered, but with rapid clinical improvement these were quickly tapered to zero during the next week. The muscle tenderness persisted and very slowly resolved under physical therapy during the next three to four weeks. Because of impairment of peripheral pulses in the lower extremities, consultation with a vascular surgeon was obtained. A joint decision was made to follow the patient closely rather than to carry out any surgical procedure designed to relieve vascular obstruction. With subsidence of the inflammation, circulation to the extremities was improved. Serial measurements of CPK remained notably elevated, and isoenzyme fractionation determined that a large fraction was CPK-2, suggesting cardiac origin. However, this was thought to reflect the high release of muscle CPK rather than indicating any myocardial disease. Findings on electromyography studies were consistent with widespread loss of muscle fiber function. At no time in the course of the patient's illness did any neurological impairment develop, and tests of renal function gave normal findings throughout the stay in hospital.

On the third hospital day, a shaking chill with fever developed, and an infiltrate was seen on x-ray films of the chest. Sputum Gram stain findings were suggestive of pneumococcal infection; this was confirmed on subsequent sputum culture. Therapy was begun with penicillin and chest physical therapy, and there was rapid response to this treatment. A second problem occurring was the development of a slowly falling hematocrit reading which reached 24 percent before starting to increase. The anemia was normochromic and normocytic without evidence of hemolysis or a bleeding abnormality. A low serum iron value was thought to be secondary to loss of iron in the form of myoglobin in the urine. Anemia was at-

tributed to the acute viral syndrome, and it fully resolved during her stay in hospital. The patient was discharged, three weeks after admission to the University of California Medical Center, with normal renal function and without evidence of leg pain, tenderness or swelling. However, it was still possible to detect muscle weakness in the lower extremities.

DR. HUMPHREYS:* Clinically significant rhabdomyolysis presents with a characteristic pattern of clinical signs and symptoms and laboratory findings, many of which were present in this patient during her illness. In this discussion, I plan to point out some of these characteristic findings and to discuss them with respect to both pathogenesis and treatment.

I would like to focus attention initially on some characteristics of myoglobin itself. Myoglobin is a heme-containing compound with a molecular weight of 17,400. It consists of a ferrohemate complex attached to a globin residue which structurally is somewhat different than the globin chains found in the hemoglobin molecule. It is present chiefly in skeletal muscle and in that tissue is present at concentrations of 2.5 grams per 100 grams dry weight of muscle. Its function in muscle tissue is not yet completely characterized, but it is thought to act as an oxygen storing and oxygen transferring compound. Of importance to the present consideration, it has been found that incubation of myoglobin at pH 5.4 results in dissociation of the molecule into its ferrohemate and globin moieties.[1] The ferrohemate complex has a molecular weight of 670 and may be able to penetrate cell membranes readily.

The differential diagnosis of pigmenturia involves chiefly the differentiation of three major entities.[2] In porphyria, the urine is positive for porphobilinogen as measured by the Watson-Schwartz test, and is negative by benzidine. In addition, the serum is clear. In both hemoglobinuria and myoglobinuria results of a Watson-Schwartz test are negative; findings are positive on benzidine test or occult blood test in the urine. Occasionally, the serum of patients with hemoglobinuria will appear pink in color, whereas serum from myoglobinuric patients will be clear. However, in many cases these criteria are not sufficient to discriminate hemoglobinuria from myoglobinuria, and so more specific measures must be used. Absorption spectrometry is a highly reliable means of discriminating between hemoglobin and myoglobin; however, breakdown of heme pigments in the urine renders this test virtually useless. A commonly employed test is that of differential filtration, taking advantage of the fact that hemoglobin has a molecular weight approximately four times that of myoglobin. Once again, this test is less than perfect, since some hemoglobin breakdown products can pass through the types of filters used for this test. Differential solubility of these pigments in ammonium sulfate has also been employed, but this test also is not specific.

Recent emphasis has been on the utilization of more specific methods such as gel electrophoresis and immunodiffusion techniques for the recognition of the myoglobin molecule. In addition, column chromatography has been employed. Whenever the diagnosis of myoglobinuria is entertained, one of these latter specific tests should be used in an effort to determine that myoglobin is the pigment present in the urine.

The clinical settings and some causes of rhabdomyolysis are listed in Table 1.[3] These can be classified broadly into the factors which alter the normal relationships between energy production and consumption in muscle, and into factors

TABLE 1.—*Causes of Rhabdomyolysis**

- Increased Energy Consumption
  - Exercise stress, heat stroke
  - Malignant hyperthermia, fever
  - Convulsions, delirium tremens, tetanus
  - Amphetamines
- Decreased Energy Production—Genetic
  - Impaired carbohydrate metabolism: phosphorylase deficiency, diabetic acidosis, hyperosmolar coma
  - Impaired lipid metabolism: carnitine deficiency
- Decreased Energy Production—Acquired
  - Potassium depletion
  - Ethanol
  - Myxedema
  - Hypothermia
  - Hypophosphatemia
- Muscle Ischemia With Decreased O_2 Delivery: K Depletion, Crush Syndrome, Arterial Embolism, Etc.
- Primary Muscle Injury
  - Polymositis, dermatomyositis
  - Trauma, crush
  - Burns
- Infections: Gas Gangrene, Tetanus, Leptospirosis, Viral Influenza, Coxsackie Infection, Shigellosis
- Miscellaneous
  - Venoms: Snake bite, hornet, brown spider
  - Drugs: Heroin, barbiturates, propoxyphene, methadone, amphetamines, licorice, carbenoxolone
  - Ethylene glycol

*Adapted from Knochel.[3]

*Michael H. Humphreys, MD, Assistant Professor of Medicine and Chief of Renal Service, San Francisco General Hospital.

which produce rhabdomyolysis through direct muscle injury. States such as exercise stress, heat stroke, malignant hyperthermia, convulsions, tetanus and amphetamine ingestion all can be associated with rhabdomyolysis presumably because the increased energy consumption associated with prolonged muscle activity outstrips the ability of the muscle to increase its energy production. On the other hand, certain genetic or acquired deficiencies in muscle energy production can also be associated with rhabdomyolysis. Included among these are muscle phosphorylase deficiency, diabetic acidosis and acquired deficiencies such as potassium depletion and hypophosphatemia. Finally, muscle ischemia with associated decrease in oxygen delivery may also result in rhabdomyolysis and can be seen in crush syndromes, arterial embolism and potassium depletion. Primary muscle injury such as polymyositis, trauma and crush injuries and burns may produce rhabdomyolysis. Infections associated with rhabdomyolysis include gas gangrene, leptospirosis and, of relevance in the case presented this morning, viral influenza. Presumably, rhabdomyolysis results from these infections through a direct damage to muscle cells. Finally, there is abroad miscellaneous category of events associated with rhabdomyolysis; the exact mechanisms by which these agents produce rhabdomyolysis are not known. In the case of many of the drugs mentioned, it is likely that rhabdomyolysis occurs as a result of prolonged coma and associated muscle ischemia.

Clinically, the systems involved in rhabdomyolysis result in a triad consisting of myopathy, neuropathy and nephropathy. Significant rhabdomyolysis will be associated with readily detectable muscle tenderness, weakness and pain. Indeed, the edema and soft tissue reaction associated with the muscle damage may be so severe as to produce compression of adjacent arteries and nerves; the weakened foot pulses present in the case reported today are an example of this. In many such patients, fasciotomy will be required in order to relieve vascular compression. It is perhaps obvious that this superimposition of additional muscle ischemia may exacerbate the clinical presentation. Neuropathy in the setting of rhabdomyolysis may occur through two mechanisms. One is by the compression of nerves passing through a restricted muscle compartment which has become swollen, edematous and tense. The other is from direct compression of nerves from prolonged coma associated, for example, with drug overdoses. Any of the peripheral nerves may become involved, but peroneal and sciatic nerve involvement is common, and abnormalities of the brachial plexus have been reported.[4] The combination of muscle and nerve involvement in an extremity may help to account for the great length of time which is generally required for normal function to be restored in such patients.

TABLE 2.—*Pathogenesis of Acute Renal Failure in Patients with Rhabdomyolysis*

1. Tubular Obstruction
2. Toxicity of Heme Pigments
3. Renal Ischemia
4. Decreased Glomerular Permeability

I would like now to turn my attention to a discussion of the third member of the clinical triad of rhabdomyolysis, namely the development of acute renal failure. This is a common and serious complication, and indeed one might legitimately question what features about the illness in the patient discussed today prevented the occurrence of acute renal failure. Four major theories have been advanced to explain the development of acute renal failure in this setting, although the exact pathogenesis has not been clearly shown. The four postulated mechanisms are listed in Table 2.

Tubular obstruction was one of the earliest mechanisms invoked to explain oliguric acute renal failure caused by myoglobinuria. This was because the presence of pigmented casts in the urine, and of casts in renal tubules observed in renal biopsy specimens, led to the speculation that excretion of myoglobin in some way caused the precipitation of proteinaceous material in the tubule and secondary obstruction.

A second proposed mechanism invoked myoglobin itself as a toxic agent for the renal tubules. Support for this mechanism was obtained from the studies of Braun and his associates.[5] They were able to show that muscle damage in rats resulting from glycerol injections produced acute renal failure which was characterized by impairment of organic acid (para-aminohippurate) and organic base (tetraethylammonium) transport. These findings were correlated with *in vitro* studies of para-aminohippurate (PAH) and tetraethylammonium (TEM) uptake by renal cortical slices. The presence of myoglobin in the incubation medium significantly decreased PAH uptake by the cortical slices, and hemoglobin and methemoglobin, in addition to myoglobin, all decreased

TABLE 3.—*Features of Myoglobinuric Acute Renal Failure*

Clinical Situation: Crush injury, burns, status epilepticus, heat stroke, drug ovedrose and others
Laboratory Findings
Urine Hematest positive, sediment without red blood cells
Urine positive for myoglobin
Hyperkalemia
Blood urea nitrogen: creatinine ratio <10:1
Hyperphosphatemia out of proportion to the degree of renal insufficiency
Hyperuricemia
Hypocalcemia early, hypercalcemia late in course
Abnormal muscle enzymes

hippurate uptake if the slices were studied after ten minutes of hypoxia or with ammonium chloride in the incubation medium. All three heme compounds reduced PAH uptake when incubated at the medium pH of 5.4, and these findings could be reproduced when only ferrohemate was added to the medium. These authors concluded that the heme pigments themselves were toxic to renal tubular function and that it was possible that the ferrohemate portion of the heme molecule was responsible for this toxicity.

A third mechanism proposed to account for oliguric acute renal failure in the presence of myoglobinuria has been that of renal ischemia. In glycerol-induced experimental myoglobinuric acute renal failure, renal cortical blood flow is decreased.[6] It is known that under certain circumstances, glomerular filtration is critically dependent on the rate of plasma flow through the glomerulus,[7] and increasing glomerular plasma flow has increased glomerular filtration rate in a model of ischemic acute renal failure in rats.[8] The factors responsible for the production of this renal ischemia are not known with certainty but may involve actions of the renin-angiotensin system and possibly the sympathetic nervous system.

The fourth suggested mechanism is more controversial. In a clinical study, Clarkson and his colleagues were able to show the presence of fibrin strands in electron micrographs taken from kidney biopsy specimens of patients with myoglobinuric acute renal failure.[9] These investigators postulated that fibrin deposition in some way led to the decreased glomerular filtration rate and the acute renal failure in this setting. Additional support for this suggestion was obtained from the experimental studies of Wardle and Wright.[10] They produced myoglobinuric acute renal failure in rabbits following intramuscular glycerol injection and found evidence for enhanced clotting activity in the glomeruli of these animals. Therefore, it is possible that intraglomerular fibrin deposition could impair glomerular permeability and thereby contribute to the pathogenesis of oliguria in this condition.

Turning now to a consideration of the clinical manifestations of myoglobinuric acute renal failure, the major features are listed in Table 3. From what has been said before, it is obvious that the clinical setting in which the renal failure occurs should be one of the first tip-offs to the possibility of myoglobinuria as the cause. Another indication comes from examination of the urine. In the presence of myoglobinuria, the urine test for occult blood will be positive but usually the sediment will be free of red blood cells. The presence of myoglobinuria can then be confirmed by measuring urine myoglobin using one of the specific tests described earlier.

The clinical course of acute renal failure in this setting is usually marked by several characteristic features. Hyperkalemia develops early and may often be the first indication to commence dialytic support for these patients. Presumably, muscle damage leads to release of large amounts of intracellular potassium into the circulation to account for the rapid rise in serum potassium. The blood urea nitrogen (BUN)-to-creatinine ratio, normally greater than 10, may be less than 10 in these patients; this is thought to be due to the release of muscle creatine or creatinine into the circulation, raising the serum creatinine concentration out of proportion to the elevated BUN level.[11] Also related to the muscle damage is the development of hyperphosphatemia out of proportion to the degree of the renal insufficiency. An associated finding is the presence of severe hyperuricemia probably due to the catabolism of muscle purines. Uric acid excretion in such patients before the development of oliguria may be notably elevated.[3]

Another common finding is the presence of hypocalcemia early in this phase of the illness. Studies have suggested that this results from release of intracellular phosphorus into the circulation, elevation of the calcium-phosphorus product and subsequent deposition of calcium salts into osseous and extraosseous tissues, including the damaged muscle. It is frequently observed that the reverse of this phenomenon can also occur—namely, that previously deposited calcium salts

are released into the circulation as muscle healing takes place—and hypercalcemia may result. This temporally often corresponds to the improvement in renal failure and the onset of the diuretic phase. The hypercalcemia observed in this setting does not cause difficulties, and usually no specific treatment other than careful observation will be required. Finally, the profound muscle disease always results in pronounced elevation of muscle enzymes, with rises in CPK being particularly striking as in the case presented today. Elevations of CPK-2 fraction, normally associated with myocardial damage, may occur even in the absence of myocardial disease.[12]

Figure 1 attempts to integrate certain aspects of the pathogenesis of acute renal failure resulting from rhabdomyolysis. It is clear that there are many possible routes which can lead to the development of renal insufficiency, and it is also possible that different routes may play different roles from patient to patient or at separate times in the same patient.

The natural history of acute renal failure in this setting is also characteristic. Initially pronounced catabolism is present, and frequent, sometimes daily, dialytic support is often required. The chief indications for dialysis are the notable hypercatabolism and the early development of significant degrees of hyperkalemia. We have seen patients in our hospital who have been virtually anuric for three to four days; this was initially thought to indicate a poor prognosis, but we now regard it as just another manifestation of the renal insult. Once the condition of a patient is stabilized with acute hemodialysis, the management becomes simpler and the ultimate outcome is good. In our hospital such patients require fewer uses of hemodialysis as a group, and the overall mortality is low.[13] It should be stressed that hemodialysis is the mode of dialysis to be employed in such patients, as a number of investigators have documented that peritoneal dialysis may be insufficient to accommodate the rapid rate of catabolism.[14]

We should perhaps at this point address a question that was raised earlier in the discussion: Why does not acute renal failure develop in some patients, typified by the case today, who have severe myoglobinuria and rhabdomyolysis? It is our experience that most patients with rhabdomyolysis and myoglobinuria in whom acute renal failure develops are also compromised in some other fashion that influences renal function. Often in such patients there has been volume depletion or a loss of plasma volume into areas of tissue damage with subsequent reduction in renal perfusion. Experimentally, volume expansion appears to minimize or prevent the acute renal failure following myoglobin release,[15] and the *in vitro* studies of Braun and his associates[5] suggest that hypoxia may potentiate the toxic effects of heme pigments in renal cortical slices. It is possible that in patients such as the woman in the case presented today acute renal failure does not develop despite significant degrees of myoglobinuria because renal perfusion is maintained, and volume depletion is not a component of the clinical presentation. On the other hand, there is a strong suggestion in the literature that acute renal failure certainly can develop from myoglobin release in patients in whom there appears to be sufficient hydration.[11] The final answer to this question remains elusive.

Related to this problem is the issue of prophylaxis and early treatment of acute renal failure in this setting. As mentioned above, volume expansion appears to be effective in minimizing experimental acute renal failure, and volume expansion with agents such as mannitol have been advocated to prevent or reverse acute renal failure in

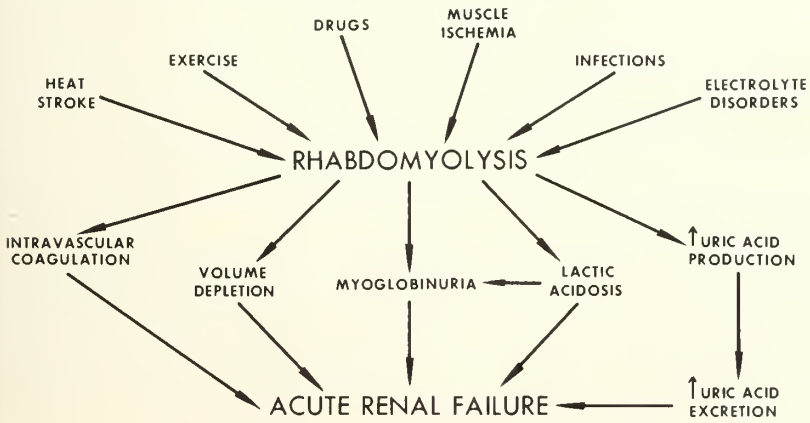

Figure 1.—Possible mechanisms by which rhabdomyolysis, resulting from a variety of causes, may produce acute renal failure.

humans. The data that have been offered to show the efficacy of this approach are controversial, and at this time there is no proven circumstance in which mannitol or furosemide administration to patients has resulted in a prompt improvement in established acute renal failure.[16]

Nevertheless, it is the policy in our hospital to do two things in patients presenting with the presumptive diagnosis of myoglobinuric acute renal failure. The first is to make sure that whatever volume depletion may be present is treated optimally with adequate fluid replacement. Once this is accomplished, we advocate the infusion of a solution of mannitol and sodium bicarbonate made by adding 2 ampules (25 grams) of mannitol and 2 ampules (100 mEq) of sodium bicarbonate to 800 ml of 5 percent dextrose in water. This reconstituted liter of solution represents roughly isosmotic fluid which will deliver 100 mEq of sodium bicarbonate per liter to the patient. Alkalinization of the urine with bicarbonate administration should enhance the rate of excretion of myoglobin and minimize its nephrotoxicity. Mannitol, in addition to producing further volume expansion, may also improve renal hemodynamics. We infuse this solution at a rate of 250 ml per hour for four hours. If at the end of that time there is an increase in urine flow rate, we continue the infusion at a rate equal to or slightly in excess of the rate of urine flow. If there is no increase in urine flow, we then consider that there is established acute renal failure in the patient and institute measures for conservative medical management. Under no circumstances do we recommend the administration of furosemide.[16]

In summary, it should be clear that rhabdomyolysis can result from a variety of different causes and clinical circumstances. The clinical presentation includes damage to muscle, to peripheral nerve and to kidney, where myoglobin or one of its breakdown products appears to be the nephrotoxin responsible for the renal damage. With appropriate medical management, however, the ultimate prognosis of acute renal failure from myoglobinuria is good.

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Important Advances in Clinical Medicine

Epitomes of Progress—Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Obstetrical Anesthesia

REGIONAL ANESTHESIA has become increasingly popular in obstetrics. With this technique, it is possible for a mother to remain awake and unnarcotized, able to participate in the birth of her baby with minimal risk of vomiting and aspiration. Continuous lumbar epidural block for regional delivery allows segmental T-10 to T-12 levels to be achieved in early labor with relatively small amounts of local anesthetic. As opposed to caudal block, the avoidance of sacral anesthesia during the first stage allows the pelvic muscles to retain their tone and rotation of the fetal head is more easily accomplished. When used for cesarean section, lumbar epidural block provides slower onset and consequently more controllable anesthetic levels and cardiovascular alterations than does spinal anesthesia.

When local anesthetics are administered to produce epidural, paracervical, pudendal nerve or local infiltration anesthesia they are rapidly absorbed from the site of injection, cross the placenta and appear in fetal blood. The clinical significance of this placental transfer depends on the blood level achieved in the fetus. Following use of relatively large maternal doses, high levels in fetal blood do occur and may cause adverse cardiovascular and central nervous system effects.

Of the amide-type local anesthetics, bupivacaine (Marcaine®), because of its high degree of binding to maternal protein, has the lowest fetal-maternal blood ratio and is probably the safest long-acting local anesthetic drug in obstetrics at present. It has been shown that neurobehavioral responses in newborn infants of mothers receiving bupivacaine epidurals are not significantly different from babies whose mothers have not been given such anesthesia. However, in some normal newborns delivered after maternal epidural anesthesia with mepivacaine or lidocaine, muscular hypotonia, diminished Moro reflexes and decreased rooting activity during the first eight hours of life have been noted. Furthermore, the neonatal half-life of bupivacaine is less than two hours while that of lidocaine and mepivacaine are four and ten hours, respectively.

When rapid onset and short duration of action are desired, 2-chloroprocaine (Nesacaine®) may be used. This ester-type local anesthetic is so rapidly hydrolyzed by plasma cholinesterase (half-life in venous blood of 21 seconds) that placental transfer of clinically significant amounts of drug is unlikely. Some anesthesiologists prefer to initiate an epidural block with 2-chloroprocaine, maintain the anesthesia with bupivacaine and then switch back to 2-chloroprocaine for the final perineal dose.

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Doses of Heparin and Protamine

HEPARIN REQUIREMENTS for cardiopulmonary bypass surgical procedures are usually calculated in milligrams or units of heparin per kilogram of body weight. However, this method of calculation may result in a seriously inappropriate dose of heparin due to wide differences between patients in their response to heparin and in the rate of its metabolic breakdown. Although variable response to drugs is common, heparin is exceptional because during surgical operation on the heart, inadequate heparinization can lead to serious, sometimes life-threatening coagulopathies.

At Loma Linda University the anticoagulant effect of heparin and its decay rate have been studied in 50 patients in whom cardiopulmonary bypass was done by measuring the activated coagulation time (ACT) of whole blood. To produce the desired activated coagulation time of eight minutes, the required loading dose of heparin differed by a factor of 3, with a range of 3.2 to 9.0 mg per kg of body weight. In the same group of patients, the half-life of heparin differed by a factor of 5, ranging from 0.8 to 4.5 hours.

This wide variability between patients insures that when the commonly used dose protocols are applied to a series of patients, some will be inadequately heparinized and others will receive much more heparin than they need.

Allowance for variations in patient response to heparin can be provided by constructing a dose-response curve from ACT measurements. Such a curve relates the clotting time to heparin dose in each patient and permits the calculation of the heparin dose required. At the completion of bypass the same dose-response curve can be used to determine how much heparin activity remains in the patient, and consequently the amount of protamine required to neutralize it.

The determination of activated coagulation time is a simple test that can be done in the operating room by relatively unskilled personnel. It permits accurate control of heparin doses and subsequent neutralization with protamine, removing the guesswork from a procedure in which a bad guess can be disastrous.

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Ketamine

KETAMINE is an anesthetic agent that was introduced several years ago with much fanfare. Initial claims for the drug were grossly exaggerated and appeared in general circulation newspapers and magazines in addition to the medical literature. Now, after the initial wave of overenthusiasm as well as a backlash phase, it seems appropriate to consider what ketamine can and cannot do.

It is clear that even though laryngeal and pharyngeal reflexes often are not depressed or not notably depressed, ketamine cannot be given safely to every patient with a full stomach without danger of vomiting and aspiration of vomitus. There have been reports of patients who did vomit and aspirate after the drug was given. Nevertheless, there is some value in the relative sparing of laryngeal and pharyngeal reflexes. Ketamine is a potent analgesic agent and does produce anesthesia. It may be useful given alone or with other agents for certain kinds of procedures. These include (1) neurodiagnostic procedures such as myelograms, ventriculograms and pneumoencephalograms where the increase in the intracranial pressure produced by ketamine is not detrimental to the patient and

(2) debridement, painful dressing changes and skin grafting, particularly in burn patients. Other situations in which ketamine may be used include diagnostic and operative procedures of the pharynx, larynx, head, eye, ear, nose, anus and mouth (if given with other agents); and certain gynecologic procedures such as dilatation and curettage. Some physicians use ketamine for cardiac catheterization, or when anesthesia must be administered intramuscularly because an intravenous site is not available. It also may be valuable as an induction agent or indicated in poor risk patients or in orthopedic procedures such as closed reductions or manipulations.

The use of ketamine has several drawbacks. One is the apparent ease with which the drug may be administered intravenously or intramuscularly for the production of general anesthesia. This has resulted in administration of ketamine by unqualified persons under adverse circumstances, without adequate knowledge of resuscitation procedures or adequate equipment available. Another drawback is increased intracranial pressure and increased arterial pressure, which may be detrimental to some patients. The drug should be used only by those skilled in respiratory and circulatory support. Another problem with ketamine is the high incidence of untoward reactions on emergence from the drug. These include hallucinations and emergence delirium, including confusion, excitement and irrational behavior. Some patients recall these sensations as extremely unpleasant and request that they never again receive this drug. The frequency with which these emergence reactions occur is said to be approximately 12 percent. Appropriate premedication with a tranquilizer may minimize the frequency of emergence delirium and diminish its magnitude. Careful attention to the circumstances under which the patient awakens, including minimal stimulation, is believed also to diminish the frequency and severity of emergence complications, but it may be dangerous for patients to be allowed to recover in darkened seclusion.

Recently the use of low-dose ketamine (that is ¼ to ½ mg per kg of body weight given intravenously, compared with 2 mg or more per kg of body weight given intravenously) has become of great interest. The available evidence suggests that emergence delirium is absent with low-dose techniques. However, additional studies are needed before this claim can be accepted with certainty.

In summary, ketamine is a valuable drug that is neither as good as enthusiasts nor as bad as its detractors claim. Each anesthesiologist must work with ketamine and after appropriate experience decide what role it will have in his practice.

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Present Status of Muscle Relaxants and Antagonists

MODERN SURGERY has benefited significantly from the introduction of neuromuscular blocking agents. Curare (d-turbocurarine) has been used clinically since the 1940's with generally satisfying results. While maintenance of skeletal muscle relaxation during surgical operation in most instances has been carried out successfully with this agent, for endotracheal intubation and for shorter surgical procedures a muscle relaxant with rapid onset and short duration of action is required. Succinylcholine, a synthetic agent introduced in 1951, fulfilled some of the requirements and was widely used. Significant side effects, however, may occur with each of these agents.

The shortcomings of d-tubocurarine are: (a) hypotension due to ganglionic blockade and occasional histamine release with associated skin reactions or rarely bronchial spasm, or both, and (b) relatively slow onset and long duration of action—the latter necessitating the frequent use of reversing agents of the anticholinesterase type (such as neostigmine and pyridostigmine). Clinical problems with succinylcholine are entirely different. This agent is not amenable to pharmacological reversal and its depolarizing action on the motor end-plate produces muscle fasciculations and muscle pains. Its duration of action depends on the rate of inactivation by plasma cholinesterase. Deficiency or abnormality of this enzyme and accidental overdose of the agent may produce extremely long lasting paralysis for which artificial ventilation is the only effective measure. Increased intraocular pressure, dysrythmias, cardiac conduction abnormalities due to potassium release, postoperative myalgia and possibly very injurious hyperthermia are additional drawbacks to the use of succinylcholine. For these reasons research continued for new and superior muscle relaxant agents.

In the United States, gallamine, a curare-like

compound with shorter duration of action, and pancuronium, with fewer side effects than tubocurarine, were introduced. Gallamine, and to a lesser extent, pancuronium, produce tachycardia. Pancuronium, because of its lack of hypotensive action currently is gaining wide acceptance. Dimethyl tubocurarine, a long known but clinically neglected agent, seems to be reentering clinical practice because of its minimal circulatory effects.

The present consensus favors introduction of a curare type nondepolarizing muscle relaxant with shorter onset and duration of action than presently available. Some compounds of this type were developed in recent years, but most of them fell short of clinical requirements. As a consequence, the reversal of the existing, longer-acting agents remains a problem of patient management.

A further variant of drug application in this field is the substitution of glycopyrrolate in place of atropine in the "reversing process." Less tachycardia and dysrhythmias are claimed with this agent during the reversing process.

Development of new rapidly acting, evanescent neuromuscular blocking agents whose intensity of action can be regulated by continuous adjustment of the rate of administration, and improvements on the techniques of pharmacological reversal of the existing agents are two realistic avenues through which optimal therapeutic conditions in this clinical field may be achieved.

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Chronic Pain Management: Developing Trends

CHRONIC benign and functional pain syndromes are yielding to pharmacologic and psychologic study to show a surprising variety of diagnostically distinct and therapeutically manageable entities.

Spinal anesthesia was applied systematically in these syndromes in the 1930's. However, this was not widely exploited until this decade as the differential spinal block. This technique utilizes intrathecal injections of solutions at ten-minute intervals beginning with a 0.9 percent solution of sodium chloride. This is followed by procaine solutions in increasing concentrations of 0.25 percent, 0.5 percent, 1 percent and 2 percent. The saline solution is a placebo and the procaine solutions sequentially block the sympathetic, somatic and motor divisions of the central nervous system. Pain which is relieved by placebo or is not relieved by paretic or paralytic concentrations is interpreted as central pain and can be further evaluated with psychologic testing. Central pain syndrome implies that the pain complaint is resistant to peripheral somatic interventions and is independent of peripheral pathology, such as laminectomy scars. Relief by placebo implies cortical control over the pain complaint.

Using this technique, Winnie reported on a series of patients with bizarre back and leg pains which were relieved by sympatholytic concentrations of procaine. This suggests either vascular problems or occult sympathalgias (reflex sympathetic dystrophies) in 75 percent of patients with pain of unknown cause. Relief by somatic block suggests an organic basis for pain. However, painful muscle spasm secondary to anxiety is relieved by somatic block although it is a reflection of a psychologic state. Differential block has resulted in a change in diagnosis in 59 percent of patients seen at the Stanford Medical Center's Pain Clinic. When the Minnesota Multiphasic Personality Inventory (MMPI) is used to evaluate central pain states further, characteristically the pain complaint represents depression, anxiety or hysteria. In patients for whom findings on psychological tests are normal, pain may be related to persistent environmental reinforcement (operant conditioning), for example, in seeking affection from an inattentive spouse. Another group in this category is existential pain in which the pain gives meaning to life often in a religious or social context. Central pain may also result from anatomic neural damage, such as tabes dorsalis or thalamic syndrome.

Phenothiazines and the tricyclic antidepressants are remarkably effective in the management of pain as a manifestation of anxiety-depression. Supportive psychotherapy is useful for hysterics, and behavior modification is helpful for patients with the "habit" of a pain complaint. In patients for whom the cause of the pain syndrome is refractory to specific treatment or is still uncertain, development of coping skills is of benefit. This

may be done through psychotherapy, hypnosis or biofeedback. Transcutaneous nerve stimulation is useful for patients with pain mediated by the somatic sensory system and selected central pain syndromes. Therapeutic nerve block retains a place in the management of active herpes zoster, acute low back pain and sympathalgias.

The most profound step in the management of chronic pain in the past decade has been to eliminate emphasis on surgical procedures and medications and develop coping resources in a patient often by exploring the meanings of pain.

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EDITORIALS

A BICENTENNIAL EDITORIAL ESSAY

Another Approach to Health Care Problems?

For the past decade the federal government has been moving into the field of health with a comprehensive and more or less coordinated attempt to regulate almost every aspect of health care from research to education, facilities, drugs, products, and the distribution and delivery of any and all services rendered by "providers." For years it had been said that if the private sector could not, would not or did not solve the evident problems in health care—uneven access, quality that was not always assured or costs that were too high—the government would have to step in to protect the public interest and the public purse. The problems were not solved to the public satisfaction and the government indeed has stepped in. However, after a decade there is little evidence that very much more has been solved as a result of this intervention.

The plain truth is that the track records of both the private sector and of the government, since it began to intervene on a significant scale, leave much to be desired. Initially there was enlightened cooperation in the field of medical science and much was accomplished. But more recently and particularly in the field of health care delivery, cooperation has been less evident and it appears to have been replaced by something more like an adversary approach. In fact this, rather than cooperation, seems to have become the order of the day, and there is a growing government concern, public disenchantment and professional dissatisfaction with what is going on and with what it costs.

It is suggested that the true nature of the health care system has really not been understood by either the private sector or the government, whose spokesmen sometimes simplistically refer to it as a "nonsystem." On the one hand the private sector has tended to believe that relatively unregulated and uncoordinated free enterprise together with a free market, if left alone, could and would solve all the problems. But more and more experience indicates that this is not the case and that it is not in the nature of the health care system to respond to these forces as do other less complex systems of industry and trade. Therefore that assumption, still held by many, seems incorrect.

The government, on the other hand, clearly believes that the health care system can be brought under control, systematized and managed by the use of laws, regulations which have the force of law, and control of funding. This assumption is now being tested on an increasingly grand scale. Yet after a decade of mounting effort, far less than the proponents expected has been accomplished—either toward solving the problems of access, quality and costs, or toward improving the health of the nation. So it seems this assumption may also be questioned. And in any case the evidence suggests that it is not in the nature of the health care system to respond well to this approach.

One aspect of the health care system that is seldom noticed is that it is a system in continuing change and the rate of change is relatively rapid when compared with other systems in our society. The bald fact may be that change in the health field is so rapid that neither the free enterprise and free market system nor any formal system of laws and regulations can ever adapt quickly enough to keep up with changes as they occur. There is considerable to suggest that this is the case, and if so it could account for much of the apparent ineptness of the present approaches. A second aspect of the nature of the health care system is the unusual degree of interdependence among its various elements. It appears that no part of it can be significantly changed without far-reaching and often significant effects throughout the system—this may be the best evidence that it is not a "nonsystem." But perhaps the most important characteristic of all is that the health care system is a thing of people. It is a thing for people and by people. It therefore reflects all of the irrationalities, assumptions, beliefs and quirks of the people who serve it and whom it serves, and this means that in many ways it is certain to be unpredictable and often inexplicable. When one takes these characteristics, their extent and their ramifications all into account, it is evident that neither of the approaches, laissez faire or controls

imposed from outside the system, are likely to work well. And indeed they have not.

What then is to be done? Clearly some new approach is needed. In this bicentennial year one's thoughts turn to early America and to the principles upon which this nation's greatness was built. In early America there was rapid change and interdependence, and life was certainly a thing of people. When there was a common problem or a community problem the approach was for everyone to turn to and deal with it. First a consensus was reached and this was followed by a will on the part of all concerned to carry out the consensus and get done what needed to be done. This was the principle of the town meeting and the way of the frontier. The decision and the action were within the system. The method worked.

One wonders if there is anything in this approach that might be applied to problems in health care today. The essential ingredients appear to be (1) agreement among all concerned that there is a problem and what the problem is, (2) a consensus or decision involving all those concerned as to what should be done and how to do it and (3) a will by all concerned to do their part to carry out the consensus or decision. These ingredients are all obviously related to one another. They are related by a common denominator—the involvement and consent of a critical mass* of all those concerned. It is the involvement, and the consent of those involved, that produces the consensus and commitment, which in turn release the will and energy to solve the problem cooperatively. This is something quite different from either laissez faire or regulatory compulsion by government. Might it be useful to try this as a new approach to some of the health care problems of today? To do so, one would have to think of the health care system (with both its private and public components) as having somehow to perform the functions of a town meeting in the sense described.

Just how this might be brought about in today's world is not entirely clear. Again it is a problem having to do with people. Perhaps to try it out, representatives of the public, the government and some major organizations in the private sector of health care might get together on an ad hoc basis. The object would not be to dwell on their differences, disagreements or adversary attitudes (which is usually the agenda or the hidden agenda of such meetings these days), but to see if they could identify and agree on a problem in health care that is relatively noncontroversial and fairly readily understood and defined. The next step would be to see if it was possible to develop a consensus as to what can and should be done about the problem—an approach to which a critical mass of those involved would consent. If this could be achieved, a broadly-based will on the part of all concerned to get it done should naturally follow and this would show itself in a cooperative rather than an adversary kind of effort throughout the system. If one or two successes, even minor ones, could be achieved in this way, a base of confidence and support might be established. There would be precedent and strength for this new approach to be tested gradually with some of the more complex problems of the health care system. If this were tried, it might signal a refreshing and even exciting start for America's third century. Will it be?

—MSMW

*The term "critical mass" is used here to express the coming together of the essential amounts and kinds of necessary ingredients to cause a reaction to take place—as in nuclear physics.

Why People Die of Iron Poisoning

THE SPECIALTY CONFERENCE on iron poisoning presented by Stein and co-workers in this issue is significant not only because of the demonstrated effectiveness of chelate therapy in iron poisoning, but because of the more integrated approach to the treatment problem achieved.

Iron poisoning has been the stepchild of iron treatment; as the use of oral iron has increased or decreased, so has the prevalence of poisoning. It is usually the youngster of two or three who discovers and consumes the brightly colored tablets prescribed by an obstetrician during the mother's pregnancy. Poisoning may follow consumption of 1 to 5 grams of iron. Such doses of iron may inflict severe local damage (necrotizing gastroenteritis) and internal damage (consumptive coagulopathy and hepatic necrosis) with clinical manifestations of acidosis and hypovolemia.[1,2] Profound mitochondrial damage occurs within cells.[3] The diagnosis is a simple matter if iron ingestion is suspected, what with a rapid test to show a plasma iron level elevated to greater than 400 μg per 100 ml[4] and a flat film of the abdomen showing radiopaque pills. The

use of desferrioxamine given orally and parenterally to chelate excess iron along with other supportive measures has been responsible for a dramatic decrease in mortality from the 45 percent reported by Aldrich in 1958[5] to none in the present series of 26 patients.

The success of treatment places greater responsibility on the health support facilities that are involved in making this medical care available with little loss in time after poisoning has occurred. The Poison Center in San Diego, for example, has provided a highly effective interphase between the lay public encountering such accidents and medical care facilities. One can anticipate an expanding role of such information facilities in answering the emergency health questions of the population at large. However, even in the best organized community, it is to be expected that early treatment of iron poisoning will not always occur, and that death will not always be avoided. The problem of prevention remains an important consideration. A reduction in the amount of iron prescribed for pregnant women (1 to 2 15 mg tablets per day taken apart from meals is ample to prevent iron deficiency), and the use of bottle tops which a child cannot easily open is also helpful.

But why do people need to keep so much potentially dangerous iron in their bathroom cabinets? It must be the consequence of an iron depleted population, of the 10 to 20 percent of menstruating women with laboratory evidence of iron deficiency and the even greater proportion of pregnant women who would show iron deficiency if not given prophylactic iron therapy. But why does the human race have so much trouble with iron deficiency?

External iron exchange in man is more limited than in other mammalian species, amounting to about 1 mg per day in men and 1.4 mg in women. The remarkable conservation of iron in itself may be a genetic adaptation to a limited iron supply and to the low availability of what iron is present.[6] Recent studies of food iron availability indicate a poor absorption of vegetal iron as compared with that of meat. It has been suggested that iron balance may have been better in Homo sapiens in the days of prehistory when man lived largely off of migrating herds, that the present day diet derived largely from the cultivation of grain is a highly artificial one. Other factors such as decreased caloric consumption and practices of food preparation also contribute to reducing iron intake. The establishment or reestablishment of an acceptable iron intake would be the definitive step to take in dealing with iron poisoning by removing the need for iron therapy. Those who express concern that fortification of food will increase the problem of chronic iron overload must give equal consideration to the deaths that occur from iron deficiency, from the complications of transfusions administered to anemic individuals with iron deficiency and from acute iron poisoning. It helps that the prognosis of both acute and chronic iron toxicity is improving through better treatment, but the underlying need for more adequate iron balance remains.

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Rhabdomyolysis

During the winter of 1975-76, at least six cases of a "flu-like" illness with evident myositis were observed in the Dallas area. All showed classical evidence of rhabdomyolysis and myoglobinuria as noted in the patient presented in the Medical Staff Conference in this issue. In several of these patients, there was acute renal failure and it is noteworthy that these were the same patients in whom pronounced vomiting, diarrhea and volume depletion were seen. Thus, in our cases as well as in those previously cited[1,2] volume depletion appeared to be the factor determining whether or not acute renal failure would supervene in the wake of myoglobinuria. Volume depletion, by increasing the concentration of the urine, would increase the concentration and presumably the nephrotoxicity of the heme pigment. Furthermore, in most patients who are volume depleted and catabolic, urine is intensely

acid. In this situation, urine of low pH could have at least two harmful effects. First, it could potentiate the nephrotoxicity of myoglobin.[3] Second, in patients with muscle injury, uric acid commonly is overproduced. Acid and concentrated urine would also favor uric acid precipitation.[4]

Such cases of myoglobinuric acute renal failure have been observed sporadically in dialysis centers for many years. Before we recognized that rhabdomyolysis was a common disorder, the cause of acute renal failure in such cases was usually ascribed to "dehydration," unrecognized shock and the like. Besides occasional cases of "flu," I have observed one patient with typical type A infectious hepatitis in whom there was evidence of significant rhabdomyolysis. Findings on studies of a needle biopsy specimen from a tender muscle disclosed patchy fiber necrosis and lymphocytic infiltration. Based upon the ever-increasing number of clinical entities recognized to be associated with rhabdomyolysis (see Table 1 in the Medical Staff Conference), it would not seem surprising that nearly all viral illnesses with a myalgic prodrome will at least on occasion be associated with frank rhabdomyolysis and, when severe, acute tubular necrosis.

In persons in whom acute rhabdomyolysis occurs, serum creatine phosphokinase (CPK) activity usually peaks within 12 to 24 hours and thereafter declines by approximately half each succeeding 48 hours.[5] In contrast, in this patient CPK activity progressively rose. This suggests ongoing necrosis and appropriately there was concern about vascular compression in the lower extremities. In patients with rhabdomyolysis affecting the legs, the initial heat and swelling sometimes subside but then become notably accentuated on the second or third day. Timely recognition of this second-wave phenomenon is critical. In these cases, a fasciotomy can save a muscle, an extremity or a nerve. Injured skeletal muscle behaves in a fashion resembling that of a subdural hematoma. As its intracellular contents decompose, the muscle accumulates salt and water. If this occurs within a tight fascial compartment, secondary ischemic necrosis can occur. To explain this phenomenon, one can envision a process whereby intracellular substances such as proteins or blood decompose into smaller fragments. Having osmotic activity, they would promote movement of water and salt from the circulation in sufficient volume to induce a pronounced elevation of hydrostatic pressure. Quantitatively, the elevated osmotic activity in a semirigid fascial compartment required to produce such an effect would be very small, that is, less than 10 mOsm per kg, since the hydrostatic pressure generated by each milliosmol is 17 mm of mercury. In some patients with this phenomenon, the erroneous diagnosis of thrombophlebitis is made. Homan's sign can be positive and many other features of phlebitis can occur.* Mistaken administration of anticoagulants could well intensify hemorrhage into the injured muscle.

It is also notable that despite apparently extensive muscle necrosis, CPK activity in this patient was only modestly elevated. In young, healthy men in whom muscle necrosis develops, CPK activities in excess of 100,000 IU per ml commonly are seen.[6] In contrast, extensive rhabdomyolysis in patients whose physical condition is poor or those with malnutrition may be associated with only modest elevations of CPK activity. Especially prominent examples are patients with alcoholic rhabdomyolysis. This is probably related to decreased CPK content of muscle.[7]

The only exception I raise to Dr. Humphreys' elegant discussion of rhabdomyolysis concerns the question of whether furosemide should be given in hope of ameliorating or preventing acute renal failure in patients with myoglobinuria. In contrast to Dr. Humphreys' recommendation, it is my opinion that furosemide may well be helpful. By interfering with sodium reabsorption in the ascending limb, it impairs the concentrating mechanism. By this means, the concentration of myoglobin in the urine would be less and accordingly there should be less nephrotoxicity. Second, by interfering with sodium reabsorption, renal tissue oxygen tension should increase.[8] This also should theoretically decrease the potential nephrotoxicity of myoglobin.[9] Of course, mannitol may exert a similar effect provided it reaches the nephron.[8]

In practice, one of the most important maneuvers in the management of extensive rhabdomyolysis is to replenish extracellular fluid deficits immediately since sizable quantities of fluid may be lost into injured muscle cells. In this sense, massive rhabdomyolysis resembles a severe burn. In some patients, up to 12 liters of saline may be required in the first 24 hours to maintain adequate blood pressure and satisfactory urine output.[10] Given a patient with myoglobinuria in

*We have measured serum CPK activity in several patients with severe thrombophlebitis. So far, it has been normal.

whom acute tubular necrosis has not yet developed, I would also favor the use of mannitol and furosemide simultaneously. On the other hand, I have become wary of using bicarbonate in these patients for two reasons. First, under such conditions, even large doses of sodium bicarbonate generally fail to alkalinize the urine. Second, systemic alkalinization with bicarbonate could conceivably favor deposition of calcium salts in injured muscle. At any rate, induction of a diuresis with mannitol and furosemide will usually serve to dilute the urine sufficiently to bring its pH above the critical value at which myoglobin nephrotoxicity should constitute a lesser problem.

Rhabdomyolysis and myoglobinuria were once thought to be medical curiosities. Automation of muscle enzyme tests have shown unquestionably that rhabdomyolysis is extremely common, and in most large hospitals it has become recognized as one of the most common causes of acute renal failure. For this reason, it behooves all primary care physicians to be alert for this potentially serious disease. Early recognition of rhabdomyolysis is critical since the measures outlined by Dr. Humphreys in the Medical Staff Conference may be lifesaving in these patients.

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CASE REPORTS

Refer to: Euler AR, Ament ME: Crohn's disease—A cause of arthritis, oxalate stones and fistulae in cystic fibrosis. West J Med 125:315-317, Oct 1976

Crohn's Disease—A Cause of Arthritis, Oxalate Stones and Fistulae in Cystic Fibrosis

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In most patients with cystic fibrosis growth failure occurs because of malabsorption or moderate to severe pulmonary disease, or both. Occasionally, growth lag is seen in patients that is disproportionate to the severity of the primary disease.

Profound growth failure is a major characteristic of Crohn's disease in children.[1] This report documents the first association of these two diseases in the same patient in the United States and shows how Crohn's disease alters the gastrointestinal manifestations of cystic fibrosis.

Report of a Case

The patient was the firstborn of male monozygotic twins. His twin died at 6 days of age from complications of meconium ileus. An autopsy documented cystic fibrosis. The patient also had meconium ileus but recovered without difficulty. His weight gain was satisfactory, having attained the 25th percentile for weight by 6 months of age. Weight and height gains improved and by 12 months were above the 50th percentile for a 1-year-old child. This growth pattern continued until 6½ years of age when recurrent spiking fevers developed. Two months later monoarticular arthritis of the right elbow developed. Arthritis of the right knee, left ankle, left knee and left wrist occurred during the subsequent 24 months. Weight decreased to less than the 25th percentile during the next two years while these symptoms continued. No changes were seen on radiographs of elbows, knees, ankles and wrists. Serological tests for rheumatoid arthritis were repeatedly negative. Rheumatoid arthritis was diagnosed by clinical findings. No evidence of chronic bronchitis or pneumonitis developed during this period of gradual weight loss. On repeated radiographs of the chest, progressive pulmonary disease was not shown.

An appendectomy for a perforated appendix was carried out at age 8½ years. An enterocutaneous fistula developed five days after the operation. Many ileocolic and ileocutaneous fistulae developed during the next seven years despite five surgical procedures to attempt fistulae resection. Arthritis and fevers continued to recur during this interval.

Two years after the appendectomy, 50 cm of bowel, including 35 cm of terminal ileum, were resected when a tender right lower quadrant mass developed. Histologic sections of the ileum and colon showed transmural inflammation with many multinucleated giant cells. Granulomas were not identified. The patient's weight decreased to below the 3rd percentile during the 12 months after the surgical procedure was carried out.

The patient was not seen and received no routine medical care for the next seven years. A regimen of pancrelipase (Cotazym®) tablets, which had been prescribed in a dose of ten tablets per day at age 10½ years, was sporadically continued during this period.

Medical care was reinstituted at the age of 17½ after a 24-hour history of hematuria, left flank pain and a temperature of 104°F (38°C). On physical examination, the patient was seen to be wasted and pale, with two enterocutaneous fistulae draining fecal material from a midline abdominal scar. Multiple surgical scars over the lower and midabdomen were present. Weight was less than the 3rd percentile while height was at the 10th percentile for a 17-year-old. Lung fields were clear and on a radiograph of the chest no acute pulmonary disease was seen but peribron-

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chial thickening was noted. Finger clubbing was present but no cyanosis. Severe left costovertebral tenderness was noted. An intravenous pyelogram showed delayed filling on the left with a radiopaque stone in the left ureter. A left pyelolithotomy was carried out and a calcium oxalate stone removed.

Temperature elevations to 38°C occurred each day for ten days after the operation, despite administration of cefazolin (500 mg every eight hours). Multiple blood cultures were sterile and no pathogens could be cultured from the sputum. No source of fever could be found and the fevers spontaneously remitted. Laboratory studies showed the following values and findings: hematocrit, 31 percent; microcytic hypochromic erythrocytes on peripheral blood smear; serum iron, 33 μg per 100 ml; total iron-binding capacity, 312 μg per 100 ml; folic acid, 30 ng per ml; carotene, 0; prothrombin time, 46 percent; serum glutamic oxalic transaminase (SGOT), 31 IU; serum glutamic pyruvic transaminase (SGPT), 29 IU; alkaline phosphatase, 192 IU; many erythrocytes on analysis of urine; blood urea nitrogen (BUN), 11 mg per 100 ml; creatinine 0.5 mg per 100 ml; electrolytes, normal; Hematest® (Ames Co.), positive stools; normal findings on electrocardiogram, and sweat chloride, 95 mEq per liter. The result of vitamin B_{12} absorption test made with intrinsic factor showed less than 0.7 percent. A 72-hour fecal fat excretion quantitation was done when the patient was taking ten Cotazyme tablets per day. It was found that 115 grams of fat per day was excreted, with an oral intake of 170 grams of fat per 24 hours (calculated absorption = 32 percent, normal = 93 percent).

Multiple small bowel biopsy specimens were taken in the region of the ligament of Treitz with a Quinton-Rubin® tube, and no abnormalities were shown by light microscopy. Findings on proctosigmoidoscopy of the rectum were within normal limits, as were results of biopsy studies of the rectum. On an upper gastrointestinal series with small bowel follow-through, multiple ileocolic and ileocutaneous fistulae were noted. Pulmonary function studies gave the following values: vital capacity, 1,901 ml (predicted 2,820 ml); forced expiratory volume in one second (FEV_1), 1,037 ml/2,595 m; FEV_1/forced vital capacity (FVC), 55 percent (92 percent). Studies of arterial blood gases showed a pH of 7.50, an arterial carbon dioxide pressure (P_{CO_2}) of 30, an oxygen pressure (P_{O_2}) of 85 and bicarbonate value (HCO_3) of 24. On chest radiographs, increased bronchovascular markings throughout all lung fields with thickening of the bronchial walls and bilateral hyperinflation were seen.

During the patient's stay in hospital, Cotazym dosage was increased to 12 tablets with each meal. A weight gain of 7 kg occurred in the three weeks after discharge. Pronounced decrease in the drainage from the abdominal fistulae resulted after this notable improvement in the patient's nutritional status. Vitamin B_{12}, 100 μg intramuscularly, is given each month and 200 mg of ferrous sulfate is taken three times a day. A diet low in oxalate-containing foodstuffs has been prescribed.

Discussion

Chronic pulmonary disease is the commonest cause of debility and growth failure in patients with cystic fibrosis.[2] Our patient's clinical course was far worse than would have been predicted from the respiratory status. Most recurrent fevers in cases of cystic fibrosis are caused by repeated pulmonary infections.[3] Our patient, who had recurrent fevers for 13 years, never has been treated for pneumonia and only rarely for bronchitis. He has never been admitted to hospital for respiratory tract disease.

Arthralgia and arthritis occur in 10 percent of patients with Crohn's disease and may be the initial manifestation of this illness.[4] Monoarticular or polyarticular arthritis without joint deformity is usual in Crohn's disease.[4] Cystic fibrosis is not associated with arthritis. Our patient's monoarticular arthritis which developed at the age of 6½ was the first manifestation of Crohn's disease. It was present for two years before any gastrointestinal symptoms occurred.

Fistula formation after surgical operation is frequent in Crohn's disease. Spontaneous fistula formation is also common and may be the initial manifestation of the disease.[5,6] Fistulae are not associated with cystic fibrosis. The prominence of these tracts in our patient is another manifestation of Crohn's disease.

Anemia is not common in cystic fibrosis because hypoxemia which is commonly present is a stimulus for erythroid cell production.[7] Many types of anemia can be present in Crohn's disease because of gastrointestinal blood loss combined with malabsorption of nutrients such as Vitamin B_{12}.[8-10] Chronic blood loss from the gastrointestinal tract and fistulae caused the iron deficiency

anemia in our patient. This further supported the diagnosis of Crohn's disease.

Bile salt malabsorption because of ileal disease or ileal resection, or both, is common in Crohn's disease.[8,10-12] This results in increased absorption of calcium oxalate. The elevated urinary calcium oxalate concentration which results from this increased absorption often causes stone formation in patients with Crohn's disease.[11-13] Bile salt malabsorption occurs in cystic fibrosis but oxalate stone formation has not been observed. Findings in studies of the surgical specimens of the ileum substantiated the diagnosis of Crohn's disease in our patient.

Cystic fibrosis is the most frequently occurring lethal genetic disease among white children.[14] Its incidence ranges from one case per 1,000 to 2,500 live births.[15] The incidence of Crohn's disease is nine cases per 100,000 in the United States.[16] The probability of these two diseases occurring in the same child is very unlikely, therefore making their association coincidental.

Summary

An adolescent patient with cystic fibrosis, anemia, fistulae, arthritis and calcium oxalate stones was proven to have Crohn's disease by microscopic evaluation of surgically resected terminal ileum and colon.

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Refer to: Dyck P, Ramseyer JC, Doyle JB: Cysticercus cyst of temporal lobe presenting as a tentorial pressure cone. West J Med 125:317-320, Oct 1976

Cysticercus Cyst of Temporal Lobe Presenting as a Tentorial Pressure Cone

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CYSTICERCOSIS is an infestation with the larval (bladder-worm) stage of a species of Taenia (tapeworm). It is a global disease, but public health measures have made it uncommon in North America[1] and most European countries.[2,3] In the United States, the Mexican-American[4] population is most frequently affected, particularly in the southern border states. We should remember, however, that tapeworm infestation is also prevalent in Asia. With recent United States involvement in that continent and increased emigration from the Orient the prevalence of this disease may also increase in our country.

Escobar and Nieto[5] have described four types of central nervous systems involvement: meningeal, ventricular, parenchymatous and mixed. The meningeal form is most common. When the basal cisterns are involved, communicating hydrocephalus results. Blindness is usually due to inflammatory scarring in the vicinity of the optic chiasm. The spinal meninges may also be affected.[6] Several hundred small cysts may coalesce and fill an entire middle cranial fossa, as has been encountered by one of the authors (P.D.). The ventricular system may be obstructed by cyst within the 3rd and 4th ventricle or at either foramen of Monro.

When the parenchyma of the brain is affected,

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there is a predilection for the cortex, apparently due to its richer blood supply. Multiple small lesions, (0.5 to 1.5 cm) are generally found. Lehmann[7] reported a case in which a moderately large lesion arose within the corpus callosum and appeared to extend into the septum pellucidum. It was described to be the size of a walnut. Death was precipitated by ventricular obstruction. We are presenting a case report of a Korean woman in whom a large solitary cysticercus cyst in the right temporal lobe was successfully treated surgically.

Report of a Case

A 38-year-old right-handed woman had complaint of intermittent headaches for six months but was otherwise well. Over a period of 48 hours increasingly severe headache, lethargy and vomiting developed, resulting in admission to hospital at the Hospital of the Good Samaritan in April 1975. No history of craniocerebral trauma, seizures or tapeworm infestation was elicited. She had emigrated from Korea to the United States six years previously.

On neurological examination, the patient was semicomatose. There was no papilledema. Right sided oculomotor paresis (including ptosis, a large fixed pupil and absent adduction of the eye), left central facial weakness, left hemiparesis, left-sided hyperreflexia and bilateral Babinski signs were noted. Periodically there was decerebrate posturing of the left upper extremity.

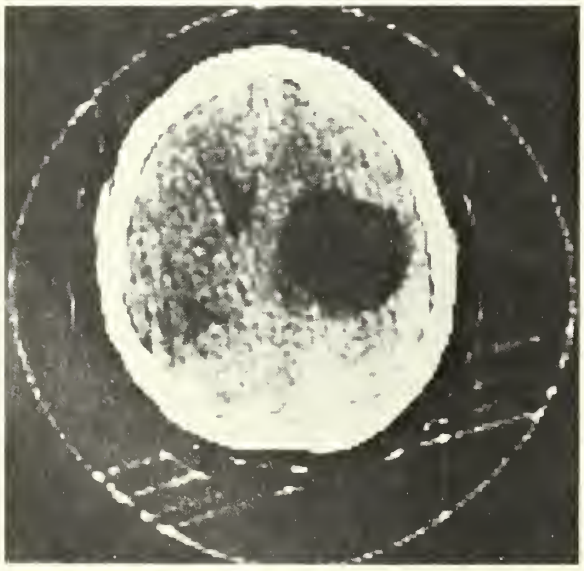

Figure 1.—Computerized axial tomography (EMI® scan) illustrates a large cystic cavity and the almost complete obliteration of the right lateral ventricle. Note the displacement of the left lateral ventricle to the left. The diameter of the parasitic cyst was 4.5 cm. The fluid contained within it has the density of cerebrospinal fluid, although there was no ventricular communication.

The patient was given steroids and an osmotic diuretic. Computerized axial tomography was carried out (Figure 1). A massive right middle fossa cystic lesion, approximately 4 cm in diameter, was shown to be present, and a parasitic cyst was suspected. Findings on angiography of the right carotid confirmed the presence of a large avascular temporal mass. No abnormalities were seen on x-ray films of the chest. There was no indication of anemia or eosinophilia.

Surgical Findings

A temporal craniotomy exposed a large middle fossa cystic lesion that was encountered at a 1 cm depth through a middle temporal gyrus cerebrotomy. The cyst fluid was clear; there were no daughter cysts within the cavity. The wall of the cyst was intimately attached to the surrounding brain. As the medial cyst membrane was being removed, several smaller lesions were noted to be externally attached to this membrane. No other visible evidence of cysticercus was encountered. The temporal lobe cavity was allowed to freely communicate with the temporal horn.

On the microscopic examination, the characteristic cuticle of a tapeworm[1] was noted, as shown in Figure 2, Left. Figure 2, Right, shows the inflammatory reaction that surrounds such parasitic cysts. Abundant lymphocytes and plasma cells intervened between the parasite and gliotic brain. This inflammatory reaction is characteristic of cysticercosis, making it difficult to resect these lesions from surrounding brain tissue.

Postoperative Course

After surgical operation the patient was alert and the oculomotor paresis gradually resolved. On the third postoperative day headache and confusion developed. Results of repeat computerized axial tomography confirmed the presence of a persistent middle fossa cavity, although it was smaller than the cyst. No significant ventricular dilation was noted. A lumbar puncture was done, the opening pressure was 600 mm of water. Enough cerebrospinal fluid was drained to return the pressure to normal. The headache disappeared, the patient became alert immediately thereafter. Repeated lumbar punctures were required for five more days. On each occasion the cerebrospinal fluid was xanthochromic and the protein level elevated.

Before discharge, soft tissue detail x-ray studies of the thigh muscles showed multiple calcifications characteristic of cysticercosis. A personality change was noted by the family members for two months after surgery, then the patient appeared to return to normal. She has remained symptom free to date. No parasites were recovered from stool specimens.

Discussion

The adult Taenia solium (pork tapeworm) lives in the lumen of the small intestine of man, attached to the mucosa by its scolex (head) with four suckers and hooklets. Gravid proglottid are passed per anum, each containing some 40,000 eggs. These eggs are protected by a porous shell, that is digested away in the stomach of hogs. This liberates the hexacauth embryo into the gut lumen. These embryos then penetrate the intestinal mucosa and are hematogenously disseminated, particularly to the muscle mass of the pig. Once lodged within the tissues of this intermediate host, the cysticercus cellulosae larvae develops within nine to ten weeks. They remain viable for about a year in hogs, then die and calcify.

When insufficiently cooked pork containing these viable larvae (measly pork) is eaten by man, the cysticerci are digested out and their scolex evaginates, thus the so-called "bladderworm" attaches itself to the intestinal mucosa and develops into an adult parasite. This completes the life cycle.

Man becomes vulnerable to systemic infestation when he replaces hogs as the intermediate host to cysticerci by ingesting the eggs in contaminated vegetables or water. Autoinfection may also occur by regurgitation of infected intestinal content into the stomach or the ingestion of eggs by the "anus to finger to mouth" route. This

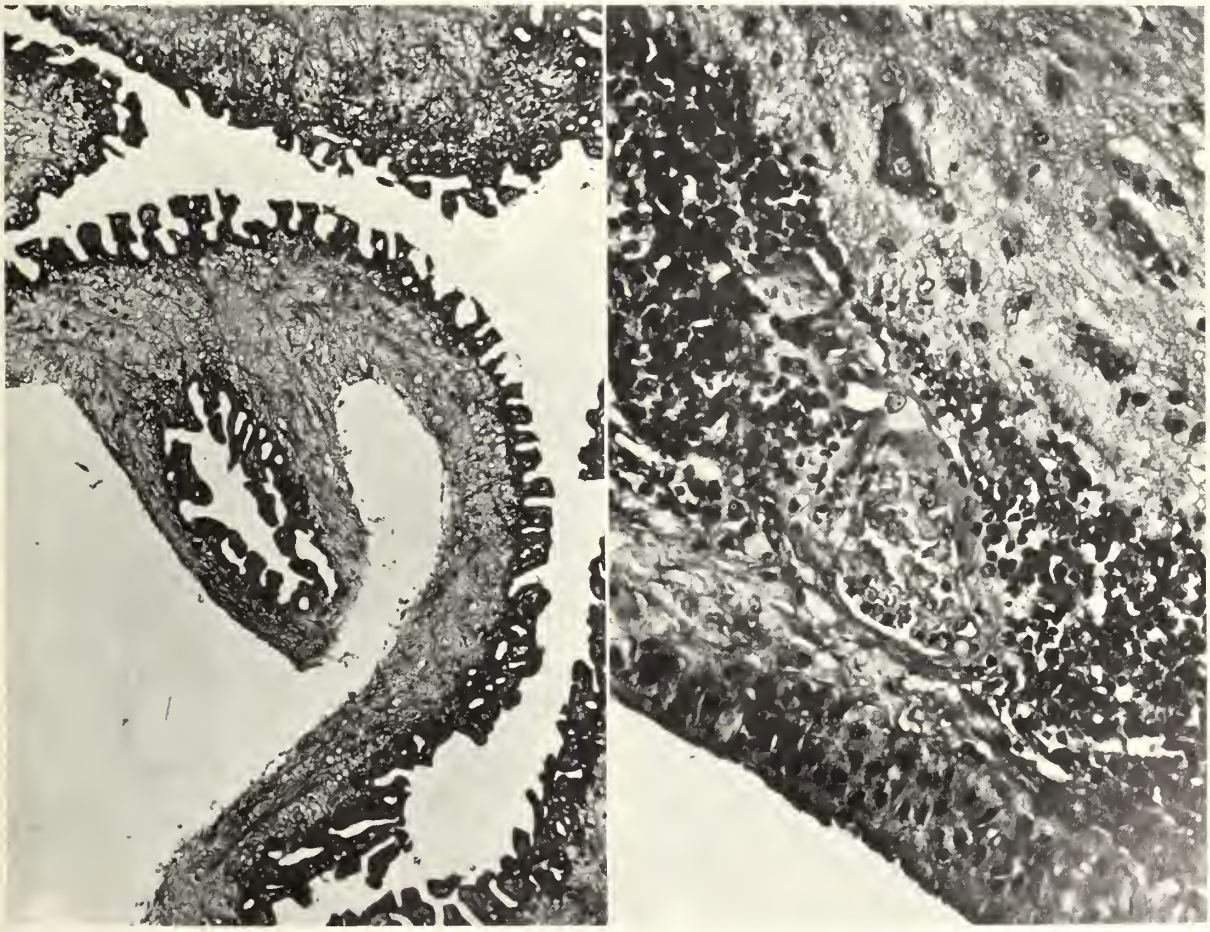

Figure 2.—Left, Shown are the characteristic microscopic features of the cuticle or membrane of cysticercus larvae. **Right,** Gliotic brain in the right upper corner of the photograph and cysticercus membrane inferiorly. Interposed is a layer of chronic inflammatory cells and hypervascularity.

latter mode of infection is particularly prevalent in children, and often leads to overwhelming and fatal disease; particularly in countries where public health standards are inadequate. Eating only well cooked pork and providing for sanitary disposal of human feces are therefore the two most important health measures for prevention of cysticercosis.

Syphilis has been called the great imitator of disease. Similarly one could consider cerebral cysticercosis as the great imitator of disease of the central nervous system. It causes convulsions, dementia, blindness, paralysis or radicular syndromes—depending on what part of the nervous system is affected. There is no specific chemotherapeutic agent available to eradicate cystocerci. However, use of steroids[4] and anticonvulsants may be clinically helpful. Hydrocephalus may be temporarily ameliorated by shunting procedures. Cabieses[9] has stated that operative excision of cerebral parenchymal cysts is fraught with difficulty, because of their multiplicity or the "impossibility of diagnosing and locating the isolated ones." The introduction of computerized axial tomography may have resolved part of this diagnostic dilemma, as our case illustrates.

Summary

A large solitary parenchymal temporal lobe cysticercus cyst precipitated uncal herniation in a Korean woman, who had lived in the United States for six years. Results of computerized axial tomography, in essence, made the diagnosis. Excision of the cysticercus cyst was followed by a gratifying result.

The presentation of cysticercosis, as a large unilocular lesion appears to be uncommon, if not exceedingly rare. We were not able to find a similar case in a review of the recent literature, and for this reason the case is being reported.

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Radionuclide Studies in Coccidioidal Meningitis

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ALTHOUGH the uniformly fatal outcome in untreated meningitis due to Coccidioides immitis has been modified by amphotericin B, use of this drug presents a challenge to therapists striving to maximize its effectiveness and minimize its not inconsiderable toxicity. Many of the complications of intraventricular therapy, using an Ommaya reservoir,[1] were encountered in a patient with coccidioidal meningitis, and this experience is reported to reemphasize the usefulness of radionuclide studies in guiding therapy and assessing the progress of the disease.[2] The examples presented may be of interest to those faced with the difficult task of treating this still dangerous infection.

Methods

Radionuclide studies were carried out with a Nuclear Chicago Pho Gamma III scintillation camera, except for the initial cisternogram and brain scan, in which a rectilinear scanner was used. Two radionuclides were used: technetium-99m labeled serum albumin initially and ytterbium-169 diethylenetriaminepentacetic acid (DTPA) after 1972. For cisternograms, 1 millicurie amounts were administered, and for ventriculograms, ½ millicurie or less. Projections and time intervals are indicated on each figure; these varied with the purpose for the examination and the route of administration of the radionuclide. Studies were done both while the patient was in and was out of hospital.

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Report of a Case

A 15-year-old white girl was admitted to hospital on June 21, 1971 after headache, nausea and vomiting developed two weeks earlier, and diplopia the day before admission. Findings on studies of spinal fluid showed 950 leukocytes per cu mm, 85 percent of which were lymphocytes; a protein content of 152 mg per 100 ml, and a glucose value of 14 mg per 100 ml. Spinal fluid cultures were negative for bacteria and fungi, but both serum and spinal fluid were reactive to Coccidioides immitis as measured by complement fixation, confirming the clinical suspicion of coccidioidal meningitis. A radionuclide brain scan showed no abnormalities, and a radionuclide cisternogram done two days after admission showed dilatation of the lateral ventricles and evidence of a partial subarachnoid absorptive block (Figure 1).

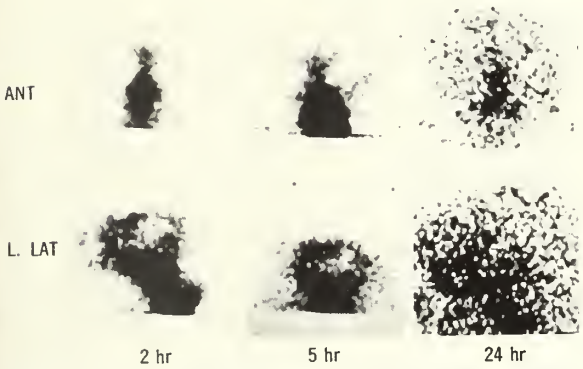

Figure 1.—Cisternogram (6-23-71). Dilated lateral ventricles and partial absorptive block indicated by delay in migration of radionuclide over the cerebral convexities.

Therapy with intravenously and intrathecally given amphotericin B was begun—intrathecal administration was facilitated by the insertion of an intraventricular cannula and Ommaya reservoir. In an attempt to determine the progress of the absorptive block and suspected associated hydrocephalus, a radionuclide ventriculogram was attempted on July 20, 1971, using the reservoir as the injection site (Figure 2). The radioactivity persisted in the reservoir, and indicated obstruction in the intraventricular cannula; the injected amphotericin B remained in the reservoir. Results of repeat examinations during the next several weeks showed partial patency between the reservoir and the lateral ventricles (after vigorous irrigation at the time of injection), communication between the ventricles and the basal cisterns, and total subarachnoid block (Figure 3).

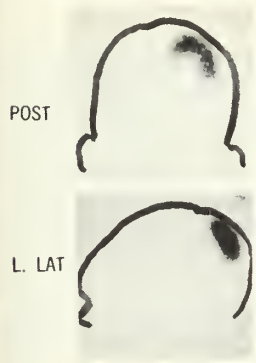

Figure 2.—Ventriculogram (7-20-71). Stasis within the reservoir, indicating obstruction in the intraventricular cannula.

Because partial obstruction of the cannula im-

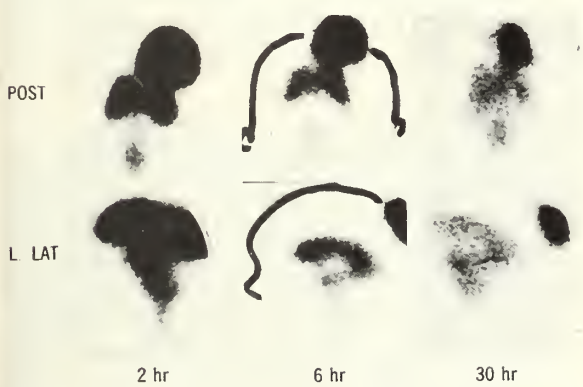

Figure 3.—Ventriculogram (8-17-71). No appearance over the cerebral convexities indicating total absorptive block. Stasis in the reservoir suggesting only partial patency in the intraventricular cannula.

TABLE 1.—*Coccidioidal Serologic Results (University of California, Davis Department of Medical Microbiology)*

	Serum				*Cerebrospinal fluid*		
	CF				*CF*		
Date	1:2	1:4	1:8	*ID*	1:2	1:4	*ID*
06-18-71	..	4+	..	+	0	..	+
06-25-71	..	..	..	..	4+	..	+
07-19-71	..	4+	3+	..	4+	..	..
08-25-71	..	4+	2+	..	3+	..	..
09-21-71	..	4+	2+	..	4+	..	..
10-31-71	2+	0	..	..	0	..	..
11-26-71	4+	..	..	..	2+	..	..
02-07-72	3+	..	..	..	0	..	..
05-22-72	+	..	..	..	0	..	+
09-22-72	3+	..	..	+	0	..	±
12-08-72	±	..	..	..	0	..	0
03-09-73	0	..	..	+	0	..	+
06-13-73	0	..	..	0	0	..	±
09-13-73	0	..	..	..	0	..	0
10-08-73	..	..	..	..	0	..	±
12-10-73	0	..	..	..	0	..	0
09-27-74	0	..	..	..	0	..	0
10-08-74	..	..	..	..	0	..	+
11-01-74	0	..	..	+	0	..	+
12-15-74	..	..	..	..	0	..	+

CF—Complement fixation
ID—Immunodiffusion
Empty spaces indicate test not done

paired the distribution of amphotericin B to the basal meninges, and with increasing mental deterioration attributed to hydrocephalus, the reservoir was replaced on August 24, 1971. At the same time, a ventriculoatrial shunt was inserted, using a medium pressure Holter valve. Despite these measures the patient remained moribund for several weeks and the prognosis seemed hopeless. Intravenous and intrathecal administration of amphotericin B was continued, however, and this effort was rewarded by a spectacular clinical response accompanied by stabilization, then decline, in complement fixation titers in both serum and cerebrospinal fluid (Table 1).

The patient left the hospital on October 15, 1971, having received 2,440 mg of amphotericin B intravenously (the total intravenous dose) and 20 mg intrathecally.

Two days after discharge, the patient was readmitted with bacterial endocarditis due to Staphylococcus aureus. During this illness, pulmonic insufficiency developed. This lesion stabilized, fortunately, and there were no subsequent deleterious cardiovascular consequences. On a radionuclide ventriculogram (November 12, 1971) free communication between the reservoir, the lateral ventricles and the shunt was shown (Figure 4).

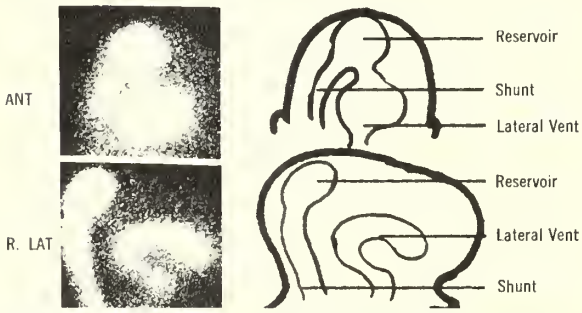

Figure 4.—Ventriculogram (11-12-71). Free communication between reservoir, lateral ventricles and shunt.

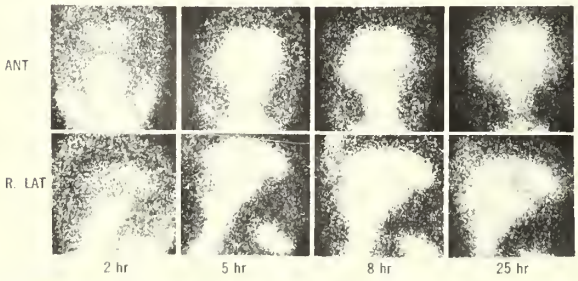

Figure 5.—Cisternogram (12-14-71). Total block at the level of the tentorium. Stasis of radioactivity within the dilated ventricles, indicative of an inoperative shunt.

Staphylococcal bacteremia necessitated a third admission to the hospital, at which time findings on a cisternogram (December 14, 1971) suggested obstruction of the shunt catheter (Figure 5). Since the catheter was suspected as the source of reinfection, it was removed and replaced. Fibrin strands were present in the distal portion of the tubing and cultures were positive for Staphylococcus aureus. The patient returned to full activities until nine months later, when a third episode of staphylococcal bacteremia required hospital admission. On a cisternogram (October 17, 1972) prompt disappearance of radioactivity from the dilated lateral ventricles was noted, in spite of a total absorptive block, indicating a functioning ventriculoatrial shunt (Figure 6). Complement fixation titers in both serum and cerebrospinal fluid had returned to normal levels (Table 1). The patient had continued to receive amphotericin B intrathecally by means of periodic injections through the Ommaya reservoir. Administration of the drug was continued until June 1973, by which time 43.25 mg had been given intrathecally.

The patient remained well for 14 months, only to be readmitted in December 1973 because of

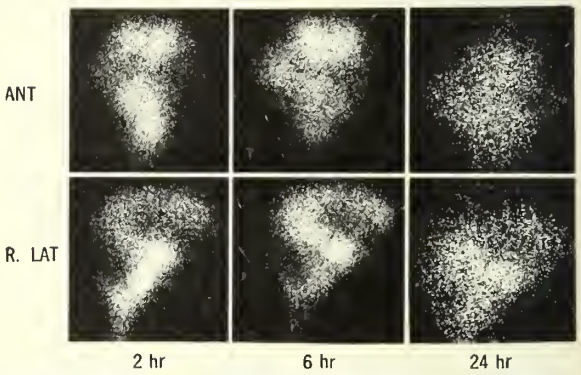

Figure 6.—Cisternogram (10-17-72). Absorptive block. Early emptying of the lateral ventricles indicates a functioning shunt.

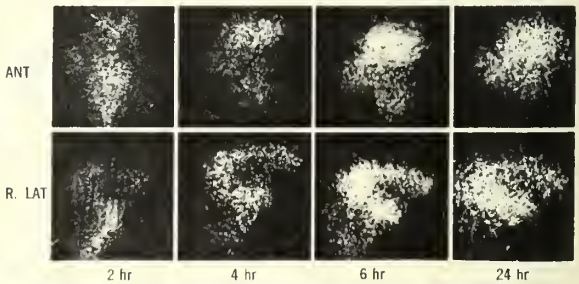

Figure 7.—Cisternogram (12-14-73). Ventricular stasis indicative of nonpatent shunt.

a fourth episode of bacteremia due to Staphylococcus aureus. Findings on a cisternogram on December 14, 1973 (Figure 7) showed stasis of radioactivity within dilated lateral ventricles (in contrast to the findings on October 17, 1972) indicating an obstructed shunt. Inasmuch as the tubing was again suspected as the source of reinfection, and since there had been no untoward symptoms attributable to hydrocephalus in spite of a nonfunctioning shunt, the tubing was removed and not replaced. Cultures from the tubing were again positive for Staphylococcus aureus.

The patient was then well and active for eight months. In September 1974, however, headache, nausea, vomiting, convulsions and fever developed; she was readmitted on transfer from another hospital with suspected relapse of coccidioidal meningitis. Studies of the turbid spinal fluid showed 120 leukocytes per cu ml (52 percent lymphocytes), a protein content of 60 mg per 100 ml and a glucose level of 58 mg per 100 ml. Cultures of the spinal fluid were sterile for bacteria and fungi, and complement fixation titers on two occasions were negative. Immunodiffusion studies[3] of the same fluid specimens gave positive results, having been negative before the relapse (Table 1).

It was felt that the findings in this case were best explained by a recurrence of coccidioidal meningitis and intrathecal administration of amphotericin B was reinstituted. An initial cisternal injection of 0.25 mg in 5 ml volume was injected over approximately two minutes. Several hours later convulsions and loss of vision in the left eye occurred. No further cisternal injections were attempted and an Ommaya reservoir was implanted to facilitate therapy. Findings on a cisternogram (September 27, 1974) confirmed the persistence of a total absorptive block and showed patency between the lateral ventricles and the spinal subarachnoid space (Figure 8). On a ventriculogram carried out on November 1, 1974, free passage of radioactive material from the reservoir to the lateral ventricles was indicated (Figure 9).

The initial clinical course was discouraging. Mental and neurological deterioration occurred despite intrathecal drug therapy (0.5 mg doses) administered approximately three times each week, after withdrawal of fluid to relieve intraventricular pressure. However, once again the patient's condition improved dramatically and the spinal fluid findings returned to normal. Intrathecal therapy was discontinued after an additional 14.1 mg of the drug had been administered. The total dose during her illness was 57.35 mg. The patient left the hospital on December 31, 1974 and has resumed her college studies. There is a residual loss of vision in the left eye, but no other neurological signs. The only medication now being given is diphenylhydantoin for prevention of seizures.

Discussion

Primary coccidioidomycosis is most common in the endemic areas in the southwestern part of the United States and northern Mexico, but sporadic cases occur elsewhere in patients who have traveled through endemic areas or have been infected from contaminated material.[4,5] Fortunately, less than 1 percent of primary coccidioidal infections become disseminated, and meningeal involvement is even less common.[6-8] It is interesting that although dissemination is more common among the dark-skinned races, the opposite is true for meningitis. Perhaps the most important characteristic of meningeal infection is the tendency to localize in the meninges surrounding the brain stem, with formation of dense inflammatory tissue that may obstruct the normal cerebrospinal

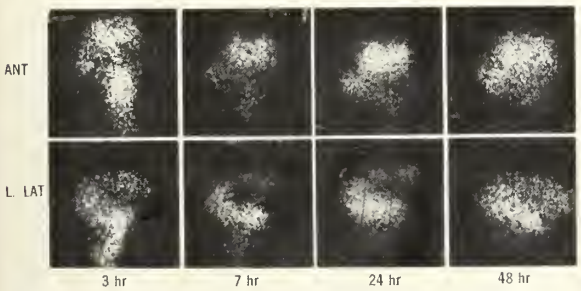

Figure 8.—Cisternogram (9-27-74). Absorptive block. Communication between lateral ventricles and spinal subarachnoid space.

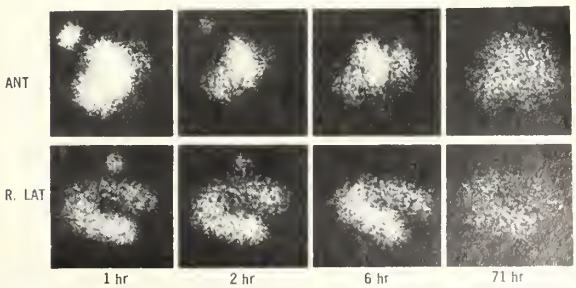

Figure 9.—Ventriculogram (11-1-74). Free entry from reservoir to ventricles.

fluid pathways and lead to communicating hydrocephalus.[6,9-14] It is thought that this complication may be prevented or minimized by early treatment,[15] although the obstruction may persist, as in the present case.

The details of the therapy with amphotericin B have been reported by Winn and others[7,16-20] and emphasize the need for both intravenous *and* intrathecal administration of the drug because of the poor penetration of the blood brain barrier. Various routes of intrathecal administration have been used: lumbar puncture, cisternal puncture and intraventricular injection. In the latter method (commonly using the Ommaya reservoir) it is essential that there be free communication between the ventricle and the cisterns to insure that the drug reaches the site of infection around the brain stem. None of these methods are without risk. Repeated lumbar instillations result in chemical arachnoiditis, and although the use of cisternal punctures appears to be safe in skilled hands,[17,18] life-threatening complications do occur.[21] One cannot exclude the possibility that cisternal administration of amphotericin B during this patient's last admission was related to the subsequent seizures and loss of vision. The present case illustrates many of the problems associated with intraventricular therapy using the Ommaya reservoir technique. An exciting innovation has been suggested that may avoid many of the difficulties inherent in repeated intrathecal injection, namely, the use of hyperbaric amphotericin B administered by the lumbar route,[16] but experience with this method is limited.

Radionuclide Studies

Cerebrospinal fluid dynamics and the movement of intrathecally injected medication are of prime concern to therapists in this disease. Fortunately, radionuclide imaging of the cerebrospinal fluid space is a relatively simple procedure and frequently studies can be done during therapeutic injections with no additional discomfort to the patient. Although generally innocuous, radionuclide cisternography does carry the risk of at least two undesirable consequences: aseptic meningitis and irradiation of the central nervous system. Since many of the procedures carried out in the case discussed were done so in the presence of active meningitis, the former complication is difficult to assess; no reactions were recognized when studies were done while the patient was afebrile. Cumulative radiation to the brain and spinal cord from repeated studies was significant. Considering all procedures, approximately 3.5 millicurie of technetium-99m and 4.5 millicurie of ytterbium-169 were administered. Assuming a dose of 60 to 65 rads to the brain surface per millicurie of ytterbium-169 diethylenetriamine-pentacetic acid (DTPA)[22,23] and further assuming a fifth this amount from equivalent doses of technetium-99m labeled albumin,[24] the patient received a total dose to the brain surface of 296 rads and to the spinal cord surface of 156 rads.[25-28] In view of the severity of the illness and the nature of the information derived from repeated studies, the risks seem justified.

The diagnostic information was instrumental in guiding the management of this patient in several ways:

- *Cerebrospinal fluid dynamics*

Both cisternography and ventriculography were useful in showing the presence, degree and progress of obstruction in the cerebrospinal fluid pathways. Early development of hydrocephalus secondary to basal arachnoiditis was suggested by findings on the initial cisternogram (Figure 1) carried out only weeks after the onset of symptoms of meningitis, and two months later complete obstruction was shown (Figure 3). On subsequent examinations the persistence of the obstruction throughout the course of the illness despite clinical remission was confirmed.

Since in this patient intrathecal medication was given through the intraventricular cannula and Ommaya reservoir, it was essential that the ventricular fluid communicated freely with the basal cisterns. This patency was shown on several occasions (Figures 3, 6, 8). Obstruction at this site would, of course, have required an alternate route of drug administration.

- *Patency of therapeutic devices*

In the course of the illness, repeated entry into the cerebrospinal fluid space was facilitated by the Ommaya reservoir and with the development of hydrocephalus, ventricular fluid was diverted through a ventriculoatrial shunt and Holter valve. Patency of the reservoir-cannula was essential for drug administration and monitoring of ventricular fluid. Obstruction in this device was shown on one occasion (Figure 2) and led to appropriate corrective measures. The functional status of the ventriculoatrial shunt was assessed on several occasions (Figures 4 through 7) and led to replace-

ment on one occasion and removal on another. The shunt itself was not commonly visualized, although it was shown to be present (Figure 4). The degree of stasis within the dilated lateral ventricles in the absence of normal migration over the cerebral convexities was a useful guide to shunt patency.

- *Drug localization*

Many of the ventriculograms done in this patient were initiated in association with therapeutic injections of amphotericin B. It is reasonable to assume that localization of the radionuclide correlated well with localization of the simultaneously injected drug, confirming that the medication was reaching the basal meninges.

Similar techniques were used to confirm cephalic migration of hyperbaric amphotericin B injected by the lumbar route.[16] These studies would be even more reassuring if the drug itself could be labeled with a suitable radionuclide and monitored by direct imaging or by *in vitro* counting of samples obtained by cisternal or ventricular puncture. Periodic monitoring of drug localization would appear to be advisable when either lumbar or intraventricular injection is used.

Summary

A case of coccidioidal meningitis is presented illustrating many of the difficulties and dangers associated with the management of this disease. Radionuclide studies can provide valuable information concerning cerebrospinal fluid dynamics, status of patency of therapeutic devices and localization of intrathecally administered amphotericin B. This knowledge is helpful, if not essential, for optimal treatment of this serious infection. Therapeutic perseverance, even in the face of a seemingly hopeless situation, can be rewarded by recovery from this serious and still fatal disease.

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Medicine and the Quality of Life

QUALITY OF LIFE increasingly is being identified as a goal of medicine and health care. In the July issue, the editors began a forum for discussing the actual and ideal relationships between medicine and the quality of life by printing seven articles expressing differing views. The following comments were generated by those articles and ones in succeeding issues.

Readers are invited to take part in a continuation of this forum by submitting their comments, written as succinctly as possible. As many of these as space permits will be published in future issues. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement to summarize the dialogue that has taken place.

The Potential of Family Medicine

LELAND B. BLANCHARD, MD, San Jose
Past President, Society of Teachers of Family Medicine

THE POTENTIAL of family medicine for enhancing the quality of life is almost unlimited. What is needed are many more health professionals applying the principles of this academic discipline to the care of people. Whereas they by no means hold exclusive rights to it, family physicians are being educated specifically to do so.

Three questions likely to be asked should be answered: What is family medicine? What is meant by quality of life? How can the one improve the other?

The emerging discipline of family medicine is concerned with the relationship of life in small groups to health and illness. In this context, family has been defined to include not only the nuclear family of father, mother and children, but any group of intimates with a history and a future. In its broadest sense, it even includes people who live alone in which case their families are relatives, neighbors, friends, co-workers and so forth.

The focus of family medicine is on the ecology of relations among individual persons both intrafamily (for example, between husband and wife, between parent and child, and among those related by marriage) and between families and their environment. Education and research in family medicine is concerned with improving *all* types of interpersonal communication. This enhances understanding between people, having the general effect of reducing emotional stress. Family medicine includes education and research to increase the distinct, unique areas of expertise that are essential to the provision of continuing comprehensive health care: prevention of illness, caring for the psychosocial aspects of illness, education and behavior modification of people to improve their health for now and in the future, and improving the health care delivery system.

Several writers in this forum have attempted to define quality of life, but I believe no one has done so to the satisfaction of everyone. I think Dr. Dubos in using the word "happiness" came the closest. Certainly one's emotional status is a vital component. Emotions range from serious depression ending in suicide at the lower end of the scale to joyous ecstasy at the upper end. Quality of life could be rated subjectively on the same scale.

Of all the concerns of family medicine, probably none has more potential for improving the quality of life than the parent-child relationship. Children learn what they live and if a child lives with approval, he learns to like himself. Can anyone think of anything more conducive to future happiness than the development of self-esteem? Only with proper parenting can this be brought about.

Unfortunately, parenting, one of the most important jobs in the world has had the least amount of research and training devoted to it. With few exceptions, unsatisfactory parent-child relationships have been the rule: either excessive affection and supervision or the other extreme of lovelessness and neglect. This type of faulty parenting results in children and then adults with a lack of emotional maturity. Later, as immature parents they say: "no so-and-so psychologist is going to tell me how to raise my kids!" Thereby a vicious cycle is established with immaturity begetting immaturity. Little wonder we find so much unhappiness in this world. This in turn leads to illness, both physical and mental, and antisocial behavior patterns. As a consequence, the quality of life for most people is not very high on the rating scale.

If enough family physicians applying the principles of family medicine could be educated so that every family could have one readily available to provide continuing comprehensive care, we could reverse this vicious cycle. Under this type of care, even immature people develop confidence in and respect for their family physician. They tend to listen to him and follow his advice. Under his guidance parents and future parents still in school could learn the cardinal principles of effective parenting. Dr. Rudolph Dreikurs in his book *The Challenge of Parenthood* presented three such principles: (1) teaching respect for order and acceptance of social rules, (2) avoidance of warfare and conflict, and (3) constant encouragement. Proper parent-child relationships could become the rule rather than the exception. How all of this could lead to increased emotional maturity and happiness and therefore improvement in the quality of life should be self-evident.

Similar reasoning is found in Dr. Lewis's statement, "Human Nature and the Quality of Life," in the August issue of this forum. Several words and sentences are selected: " . . . a 'place' or sense of belonging, confidence and self-love." "Physicians need to be educated in human nature and about how human beings work." And "Those physicians and teachers handling young children might do well to participate with parents in the way that young children are managed according to the principles of human nature derived from history and described by social and biologic psychologists."

Family medicine *may* have had its beginnings in the United States and Canada but one finds it now being promoted and taught in many other countries. As an academic discipline it lends itself to being made international. Its concerns are not limited to the parent-child and physician-nuclear family relationships, but as stated before, they include *all* interpersonal relationships, even between people of different countries. In this context, the family of family medicine becomes the family of

man. Just as a cardinal principle for improving the parent-child relationship, as previously stated, is to avoid warfare and conflict, this would naturally become a dictum for improving communication, understanding and relationships between people throughout the world. An idealist's dream? Perhaps. Impossible? Not if we can develop widespread teaching and application of the principles of family medicine.

A number of organizations as groups, and individual members within them, are devoting much time, thought and effort toward promoting family medicine: The Society of Teachers of Family Medicine (international); The American Academy of Family Physicians; the American Board of Family Practice; the Residency Review Committee for Family Practice; the American Medical Association's Council on Medical Education; the Family Health Foundation of America; the Department of Health, Education, and Welfare; departments of family medicine in medical schools; family practice residency programs in academic health centers, community hospitals and military hospitals, and others. Much is being done, but much more needs to be done before family medicine will reach its full potential for improving the quality of life.

Refer to: Blanchard LB: The potential of family medicine, *In* Medicine and the quality of life—A forum. West J Med 125:326-327, Oct 1976

A Regeneration of Hippocratic Responsibility

RICHARD A. RAWSON, MD, Palo Alto

In the quality of life forum in the August issue Dr. Peter Lewis points to a sense of history about human nature as an integrating focus for medicine and the quality of life. Apropos of this is the growing interest in ancient, "nonorthodox" modes of healing, particularly psychic healing. With the ground swell of interest in religious, spiritual and psychic activities is a growing number of physicians who have explored psychic phenomena, for their patients and for themselves. The adventure encompasses a range of emotions and reactions, not the least of which are hope, fear, belief, skepticism and wonderment. From reports, personal and anecdotal, a recurring theme is that of a transformation in quality of life.

The staff of Aesculapius, official symbol of the American Medical Association, reminds us of the historical tradition of medicine and refers to the mystical basis of healing. In medical school I safely ignored this knowledge. Now I and many other physicians surreptitiously, and in apprehension of abandonment if not censure by our "straight" colleagues, are exploring what the AMA symbolically declared itself to stand for. Hippocrates was an Aesculapian priest who introduced Greek rationalism to an art heretofore intuitive, and thus only indirectly represented in symbols. As physicians are we not now involved in a renaissance of intuitive clinical skill in a matrix of almost overpowering rationalism?

The staff of Aesculapius and its ancestor, the caduceus, or wand of Hermes, are ancient symbols of psychic, metaphysical power. In mystical tradition, the serpent is the symbol of Logos, a holy word, reason, thought—the controlling principle of the universe as manifested by speech. The staff is symbolic of the *vital life force* (Hipprocrates), the transphysical force essential to life. The seven crossings of the staff by the serpent are symbolic of the seven major psychic energy centers (Hindu: chakras) associated in function with the sympathetic nervous system. Well-being is the balanced flow of energy through these centers in the integration of Logos and the vital life force with the parallel manifestation of peace and harmony in the physical universe. As physicians we are all healers, operating on physical, mental and psychic levels to restore holistic harmony.

An aversion to our mystical heritage surfaces in the apprehension of magic and superstition, which rationalism in medicine was to have corrected. Medicine like politics and religion, is a fertile field for the temptation to use a "higher power" to force an effect. Rationalism seems no less a psychic "power" subject to egoistic abuse and with results no less dreary than superstition. Many of us have found ourselves sequestered in a biophysical scientism, suffering the rates of malpractice, alcoholism, drug abuse and suicide—severed not only from the roots of our tradition but also from the roots of our consciousness.

The integral of medicine and quality of life is an advanced responsibility of a society and of a profession which is *now* manifesting many thousands of years of accumulative experience. Physicians have chosen a role that inherently straddles the rational and the intuitive, the profane and the sacred. In a regeneration of Hippocratic responsibility each physician is creating individually a role in a "new" age which can only come from his level of personal responsibility and which we must share collectively. It is exciting and gratifying that The Western Journal of Medicine in establishing this forum has provided a means to share.

Refer to: Rawson RA: A regeneration of Hippocratic responsibility, *In* Medicine and the quality of life—A forum. West J Med 125:327, Oct 1976

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Parasitic Infections Among Traveling Students

To the Editor: As the world is made smaller and smaller by jet travel, and higher education, once a luxury, becomes almost a necessity, institutions such as the University of California attract students from all over the world. At the University of California, Davis (UCD), the international students make up about 7 percent of the student body or about 3 percent of the population of Davis. In the exchange of cultures and friendships, it may be interesting to find out how much sharing of microbes also occurs.

We have been conducting blood and fecal surveys at UCD for the prevalence of endoparasites among international students and American students who have just returned from spending a year abroad. Blood specimens were examined for the presence of microfilariae by Knott's concentration technique, and for malaria by examining a thick and a thin Giemsa stained smear. Fresh fecal specimens were examined by direct smears and the acid-ether concentration method. In the 140 fecal specimens submitted by students entering UCD in the 1974 fall quarter, we found the parasitic infections shown in Table 1.

TABLE 1.—*Parasitic Infections Found in Fecal Specimens*

Protozoan cysts trophozoites	
Entamoeba histolytica	3 (2%)
Entamoeba coli	15 (11%)
Entamoeba hartmanni	4 (3%)
Giardia lamblia	3 (2%)
Endolimax nana	6 (4%)
Iodamoeba butchlii	2 (1.5%)
Trichomonas homonis	2 (1.5%)
Helminth ova	
Ascaris	2 (1.5%)
Clonorchis	3 (2%)
Dicrocoeliid	1 (0.7%)
Enterobius*	1 (0.7%)
Hookworms	6 (4%)
Hymenolepis nana	1 (0.7%)
Schistosoma mansoni	1 (0.7%)
Strongyloides	1 (0.7%)
Trichostrongylus	2 (1.5%)
Trichuris	17 (12%)

*Adult; ova not usually in feces.

The total number of positive findings on specimens was 48 of 140 (34 percent). The blood examinations yielded only a single but significant finding, that of a Plasmodium malariae infection. We wish to point out that these were the results of only a single examination per student; multiple specimens might have uncovered an even higher percentage of positive cases.

Since many of the parasites found are potential pathogens, and some, such as malaria, are of public health importance, treatment was administered by the clinicians at the Student Health Center, UCD, to the infected persons.

We realize that this was but a small survey conducted in a small college town; however, the importation of parasite populations (diseases) through the influx of migrant workers and foreign immigrants to the West Coast can probably be extrapolated from it. It behooves us to alert medical practitioners in our area about the prevalence of parasitic diseases they may encounter in their practice. Considering the protean nature of the manifestations of various parasitic infections, differential diagnosis ignoring these diseases, which might be thought exotic, would be unwise. As suggested by Dr. David Sencer (in his delivery of the 33rd Charles Franklin Craig lecture in 1968) "in this shrinking world one of the first questions that should be asked in taking the medical history is, 'Where have you been?' "[1]

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The Recent "Estrogen Episode"

To the Editor: If any of us ever doubted the power of the news media—TV, magazines, newspapers—these doubts were certainly dispelled during the recent "estrogen episode." All physicians, but especially gynecologists, could not help but be impressed, and distressed, by the panic these news releases inspired in our menopausal patient.

And surely many of us felt a creeping sense of guilt. Had we, in our efforts to allay the distressing symptoms of the climacteric, the hot flashes, the night sweats, the dry vagina, betrayed our patients and subjected them to horribly increased hazards of cancer?

Our telephones were kept busy and our office visits grew longer as we tried to explain to our patients, and to persuade them and ourselves that some of this information was taken out of context, and that the final answer was not yet available. But even so, the doubts lingered.

It was, therefore, with great relief that we read Doctor Gordon's discussion on "Postmenopausal Osteoporosis" (Medical Staff Conference, University of California, San Francisco. West J Med 125:137-142, Aug 1976). It was, of course, good to have the positive reenforcement of our belief that "small prophylactic doses of estrogen prevent this bone loss." But even more reassuring to physicians and patients deeply concerned about the apparent increase in endometrial cancer were these two statements by Doctor Gordon:

"There is no evidence of increased mortality from endometrial carcinoma" but that "These data [increased use of exogenous estrogens in women with endometrial cancer] undoubtedly reflect increased detection."

He goes on to suggest that "estrogen-induced . . . bleeding will predictably increase the detection of early endometrial carcinoma and should thereby reduce mortality, just as the Papanicolaou smear did for cervical cancer."

This is good news that probably won't be snapped up by the news media. But a weight has been lifted from the practicing physician's shoulders. And would it not be wonderful if a similar modality could be found that would cause other cancers to bleed, or to speak out somehow, so as to enable us to achieve early diagnosis and cure?

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In Support of Physician's Assistants

To the Editor: I am responding to the letter by Dr. Eugene Felmar in the June issue [Felmar E: Physician extenders opposed (Letter to Editor). West J Med 124:509, Jun 1976]. Especially in this bicentennial year, I would not contest Dr. Felmar's right to state his beliefs in print, even though they are based on misconceptions about physician's assistants (PA). However, I would like to add my views, which perhaps are better grounded in fact.

To begin with, the term "barefoot physician" —which Dr. Felmar equates with PA—is a name made popular in this country as a result of the publicity surrounding Richard Nixon's visits to China. Recently, that term, as well as PA, has been applied to foreign medical graduates (particularly those of Vietnamese origin who came to America during our airlift operations) who are waiting to take their examinations in this country.

The physician's assistant concept, on the other hand, is a very old one. It started in Western Europe with the idea of providing medical care in rural areas, to the poor and underprivileged, and in Europe's colonies; for example, those in Africa, India and Hong Kong.

In the United States, statistics showed a population increase in the late 1960's in contrast to the constant, fixed number of medical school graduates each year. The Vietnam conflict at the same time was producing large numbers of returning veterans, many of whom were well-trained medical corpsmen who had had to provide care in combat without a physician present.

Several leaders in the medical profession felt that these corpsmen represented a manpower resource that might help resolve the national health insurance stalemate. Dr. Eugene Stead was the first to found a PA program (at Duke University School of Medicine). Since then the number of PA programs continues to grow (Yale, Bowman Gray, Texas, Nebraska, Baylor, Stanford, UCLA and others). It may be interesting to note that the national average education for PA's is somewhere between two and eight years of college, before entry into a PA program.[1-3] Future PA's, once accepted in a program, spend countless hours in classrooms studying such subjects as anatomy, physiology, biochemistry, microbiology, physical examination, clinical diagnosis, cardiology and hematology before clinical rotations. The next year is much like an internship, full of miniresi-

dencies in each specialty of the hospital; for example, internal medicine, pediatrics, surgery, ophthalmology, ENT, orthopedics, psychiatry, Ob/Gyn. Our professors during this two-year period are all MD's.

The concept as a whole has remained constant, as graduating PA's go out to give a helping hand to their physician employers primarily in small suburbs and rural communities. They are under physician supervision, and only undertake those tasks they are qualified to perform.

PA's must take a three-portion examination given by the National Commission for Certification of Physician's Assistants (the American Medical Association and the National Board of Medical Examiners are just two of the members of this commission). This is to become certified (PA-C). In order to be recertified, PA's must maintain their continuing medical education—100 hours every two years, 40 hours of which must be category I (American Medical Association, American Academy of Family Practice, American Academy of Physician's Assistants [AAPA]). Most PA's join local, state and national (AAPA) organizations much like those to which their physician employers belong. PA's also subscribe to medical journals and read new textbooks because they have a firm belief that the medical care they are involved in providing should be the best possible.

Many medical authorities have stated that we still face shortages in primary care. This is quite obvious today in the military. I work at the second largest Air Force hospital, yet we only have one full-time emergency room physician and one full-time general practitioner. With 300 patients seen each day, it would be very difficult for them to manage without the help of three PA's and one nurse practitioner. If they tried, they would have to practice the "second rate medicine" that Dr. Felmar wishes to avoid.

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Refer to: Glover D, Gerety M, Bromberg S, et al: Diethylstilbestrol in the treatment of rape victims. West J Med 125: 331-334, Oct 1976

Special Article

Diethylstilbestrol in the Treatment of Rape Victims

DIANNE GLOVER, BA; MEGHAN GERETY, BA; SHIRLEY BROMBERG, BA; SUSAN FULLAM, BA; PETER DiVASTO, MA, *and* ARTHUR KAUFMAN, MD, *Albuquerque*

Despite growing controversy surrounding its use as a "morning after pill," diethylstilbestrol (DES) is prescribed liberally for rape victims. Guidelines for its use in these patients is lacking. Of 150 consecutive rape victims treated at a university medical center, 63 (42 percent) received prescriptions for DES. Of the 55 (87 percent) on whom follow-up was obtained, in 40 (73 percent) there were substantial side effects—nausea or vomiting, or both. At least six (11 percent) did not complete therapy because of these side effects.

The authors offer guidelines for use of DES for rape victims and a plan for patient education and follow-up.

THERE HAS BEEN growing interest in the medical community in improving the health care of rape victims.[1-3] A chief medical concern during emergency treatment of these patients is prevention of pregnancy. This is usually accomplished in susceptible patients by the prescribing of high doses of diethylstilbestrol (DES), a synthetic estrogen commonly used as a "morning after pill."[4]

However, recent concern about the use of this drug has been voiced from many quarters—the health profession,[5] lay groups,[6] and government.[7] This concern springs from the results of recently published research implicating DES with subsequent vaginal tumors in female offspring of mothers who took the medication during pregnancy.[8]

The Food and Drug Administration has consequently called for more stringent criteria for use of DES, including the recommendation that should a patient taking DES subsequently discover herself to be pregnant, pregnancy termination be strongly considered.[5]

Historically, rape victims served as the original experimental group in whom DES was tested as a postcoital contraceptive.[9] With tightening controls and narrower indications for use of DES, the Food and Drug Administration (FDA) and congressional critics may in the near future allow its liberal use only in such extreme circumstances as rape, leaving rape victims one of the few groups for whom DES is routinely prescribed.

In light of this growing concern about the use of DES, a careful clinical review of experience with this drug in the emergency management of rape victims is in order.

Methods

For the past 12 months the Department of Family, Community and Emergency Medicine of the University of New Mexico School of Medicine has developed a program to improve the

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Submitted February 23, 1976.

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ABBREVIATIONS USED IN TEXT

BCMC = Bernalillo County Medical Center
DES = diethylstilbestrol

crisis and follow-up health care of rape victims and their families at the Bernalillo County Medical Center (BCMC) in Albuquerque.[2]

Under the new program, when a rape victim comes to the emergency room, a member of the department's Rape Contact Team, on 24-hour call, is immediately notified. The team member comes to the emergency room and counsels the victim, preparing her for medical examination by a gynecologist and possible questioning by police. The team member stays with the victim throughout the emergency room experience. Follow-up appointments to the Family Practice Clinic are made within two to three days to assess emotional progress, physical status and compliance with medication regimens. If victims fail to keep appointments they are either given new appointments or an attempt is made to establish contact by telephone or home visit.

Gynecologic examination of rape victims in the emergency room is carried out by gynecology residents rotating through the inpatient obstetrical service. During the time covered by this article no firm criteria guided the resident's prescribing of DES for victims of rape. Major side effects (nausea, vomiting, altered menses) and potential hazards (if pregnant) of DES therapy were generally described to each patient to whom the medication was offered. The patient herself made the final decision concerning its use. When prescribed, the dose of DES was 25 mg given orally twice a day for five days. In most instances an antiemetic medication, prochlorperazine (Compazine®) or trimethobenzamide (Tigan®), was prescribed prophylactically to diminish nausea.

Rape Contact Team members kept careful records of 150 consecutive rape victims treated at the BCMC. Doctors' prescribing patterns for DES and patients' compliance with and reaction to the prescribed drug were recorded. Since most of the patients received the full extent of their follow-up care within a week after initial emergency room contact, data on long-term reactions to DES in this population are scant and not reported here.

TABLE 1.—*Reasons DES Not Prescribed*

	Number	*Percent*
Victim using birth control	34	39
No vaginal penetration (other sex acts committed)	14	16
Premenarchal or postmenopausal	12	14
"Safe" time in menstrual cycle	7	8
No sperm seen in vaginal pool	7	8
Seen more than 72 hours after rape	6	7
Suspected pregnancy before rape	4	5
Refused DES	3	3
TOTAL	87	100

TABLE 2.—*Early Side Effects to DES*

	Number	*Percent*
No reaction	15	24
Nausea alone	23	37
Nausea and vomiting	17	27
No data available	8	13
TOTAL	63	101

Results

Of the 150 rape victims seen, 87 (58 percent) did not receive (DES). The reasons are listed in Table 1.

Of the 63 victims (42 percent) for whom DES was prescribed, follow-up information on patient compliance and drug side effects was obtained in 55 (87 percent) (Table 2). In 40 of these victims (73 percent) there were substantial side effects from DES therapy. In six (11 percent) reactions of such severity occurred that the course of DES could not be completed despite the addition of antiemetic medication. Most patients who experienced nausea noted its tendency to subside spontaneously by the second or third day, frequently disappearing completely.

In two patients receiving prochlorperazine as a prophylactic against nausea, severe dystonic reactions developed necessitating both emergency treatment of the reaction and cessation of administration of the antiemetic drug.

Discussion

Kuchera[10] reported the incidence of side effects in a sample of 1,000 women receiving DES as a postcoital contraceptive (few rape victims were included) to be 55 percent. These side effects consisted almost exclusively of nausea and vomiting. Such side effects occurred in a substantially higher proportion (73 percent) of rape victims receiving DES in our study.

It is tempting to speculate that the emotional upset of sexual assault magnifies the side effects of DES. However, Hall,[11] reporting on experience

with the use of DES in 71 women at a college health clinic (presumably few of the patients being rape victims), noted that in 71 percent nausea or vomiting or both developed, a rate similar to our own. Spontaneous subsidence of nausea over several days has been well documented.[10] This fact should be noted for each patient receiving DES.

An important outcome not reported in either of the above studies is the rate of failure to complete the full course of treatment with DES because of these side effects. Our services uncovered the fact that at least 11 percent of patients did not complete DES prophylaxis. This rate must be considered by physicians when recommending this medication.

Diethylstilbestrol (DES) is a synthetic estrogen often prescribed by doctors to prevent pregnancy after intercourse has taken place. Because of its many side effects and possible dangers, it is only given to women requesting it in emergency situations such as rape.

HOW DOES IT WORK?

High-dose estrogen like DES (50 times the normal woman's own output of estrogen) seems to change the inner lining of the uterus (womb) so that the fertilized egg passes out of the uterus and pregnancy cannot continue.

HOW EFFECTIVE IS IT?

Reports show that if the woman begins taking the drug within 72 hours after unprotected intercourse, and takes all the pills, far less than 1 percent will become pregnant. However, if DES is not taken there is a 2 percent to 5 percent chance of becoming pregnant. The closer intercourse occurs to the middle of the menstrual cycle (about two weeks before the beginning of the next period), the greater the chance of pregnancy.

HOW IS IT TAKEN?

The term "morning after pill" is misleading. Actually one must take five 5 mg tablets of DES twice a day for five days. A woman thus takes a total of 50 tablets or 250 mg over five days. Because nausea and vomiting are such common side effects, most doctors will prescribe another medicine to treat this.

WHAT ARE THE SIDE EFFECTS?

More than seven of ten women taking DES will have one or more of these side effects:

1. Nausea and vomiting (This usually subsides within two to three days)
2. Headache
3. Menstrual irregularities
4. Breast tenderness

As with all hormone-containing birth control methods, one should watch for the following symptoms:

1. Severe headache or sudden blurred vision (may mean a blood clot in the brain)
2. Severe leg pain (may mean a blood clot in the leg vein)
3. Chest pain or shortness of breath (may mean blood clots in the lungs)

Recent studies have shown that when pregnant women took high doses of DES for a long time, daughters from those pregnancies had a far greater than average number of tumors of the vagina. This has caused so much concern that it is now strongly recommended that if a woman taking DES is later found to have been pregnant or becomes pregnant despite DES treatment, abortion should be strongly considered. If the menstrual period is two weeks late after taking DES, a pregnancy test should be done. There is no evidence that a short course of DES causes any long-term harm in the woman herself.

WHO SHOULD NOT RECEIVE DES?

1. Women who know they are pregnant
2. Women who have tumors of the breast or reproductive organs or who have strong family histories of these cancers
3. Women who have had vein clots (thrombophlebitis)

Figure 1.—Information sheet for rape victims about diethylstilbestrol (DES)

The physical and emotional trauma of rape is so severe that health workers try to alleviate suffering by all possible means. This attitude has tended to favor a more liberal use of DES for rape victims in the belief that the discomfort of nausea and vomiting is a lesser evil than suffering the risk of an unwanted pregnancy and abortion.

Almost all victims taking DES voiced a strong desire to rid themselves of the physical and emotional vestiges of the sexual assault. They considered pregnancy prevention very important. In many cases, fear of pregnancy was the main reason for their seeking medical attention.

However, on follow-up visits, many victims and their health providers found that the victim's prolonged nausea and vomiting drastically interfered with their ability to return to normal function and greatly compounded their already severe emotional distress, complicating the treatment effort.

Conclusion and Recommendations

There is no absolute indication for use of DES as a postcoital contraceptive in the emergency management of a rape victim. The decision to employ this drug must be made after allowing the patient to weigh the risk of pregnancy and abortion against the likelihood of DES side effects. The physician's role is to offer options.

In light of the above findings we offer the following recommendations:

- DES should be offered as an option to every fertile, unprotected female rape victim if she is seen within 72 hours of the assault, if the assailant's penis penetrated her vaginally and if she is in the intermenstrual phase of her cycle. Though failure to find motile sperm in the vaginal aspirate or noting that the patient is near to her menses diminishes the risk of pregnancy, this risk is not eliminated. The patient should be allowed to weigh these risks and come to her own decision about taking DES.
- Every rape victim for whom DES is prescribed should receive a simply written handout describing the drug, how it is taken, the likelihood of side effects and the potential dangers to the unborn fetus. A sample currently in use at the BCMC emergency room is provided (Figure 1). It should be noted that while the FDA has ordered that each prescription of DES be accompanied by a patient booklet setting out warnings and instructions in greater detail, such booklets have not yet been developed.
- Each rape victim receiving DES should be contacted within 48 to 72 hours of beginning the medication to assess the presence and degree of side effects, the impact of DES on daily activities and feelings about continuing the medication.
- If an antiemetic is prescribed prophylactically with DES, use of prochlorperazine should be avoided because of its relatively high rate of side effects.

The physician should offer the patient clearly understood, realistic alternatives and early, supportive, follow-up care. Doctor-patient rapport will be enhanced in this way and, should side effects to DES occur, knowledge of their presence will be shared with the physician, leaving the patient less frightened, upset and alone.

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Medical Information

Refer to: Mack JW, Takamoto RM, Jones FR, et al: Toe tourniquet syndrome (Medical Information). West J Med 125: 335-336, Oct 1976

Toe Tourniquet Syndrome

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THERE HAVE BEEN several reports in the recent literature describing the strangulation of appendages by hair or thread in infants and young children. This appears most commonly to affect the toes of children wearing leotard-type clothing. The previously unreported problem of rotation of the partially amputated toe-tip after removal of the constricting hair was observed in a patient recently treated. It was felt that stabilization of the toe-tip by some means would be advisable in order to prevent this rotation. A second patient who had several hairs wrapped around the middle three toes of the right foot was seen later, and a single tacking suture of 5-0 nylon was placed with satisfactory in-line healing of the toe.

Reports of Cases

CASE 1.—An 11-month-old, black-haired, white girl was brought to the emergency room by her mother who stated that over the preceding week she had noticed that one of the child's toes had been gradually swelling and had turned a bluish color. The mother noticed a deep cut across the toe with a hair or thread projecting from it; she had attempted to remove it but was unsuccessful. The patient was referred to the surgery clinic where the fourth toe on the left foot was found to be swollen and dark colored, with a deep, circumferential laceration proximally from which a fine black hair was projecting (Figure 1). Upon exploration of the depths of the laceration the hair was found to be wound around the toe several times. The hair was unwound and found to have encircled the toe three times. The child was followed at frequent intervals and rapid healing of the laceration was seen with resolution of the swelling and return of color. After three weeks the toe was completely healed with only slight discoloration (Figure 1). However, it was noticed that the soft tissues of the nearly amputated tip had rotated, shifting the nail in a medial direction so that it was abutting the adjacent toe as shown. Otherwise the child has done well.

CASE 2.—A 5-month-old white boy was brought to the pediatric clinic by his mother after she had noted discoloration and hair wrapping around the middle three toes of the left foot. The patient had a history of wearing footed sleep wear. On physical examination, hairs were noted

Figure 1.—(Case 1) Toe tip not stabilized showing resultant rotation.

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wrapped around the middle three toes of the left foot (Figure 2). Several hairs were unwound from the toes and it was found that the third and fourth toes were most severely involved with hair wrapped several times to the bone. Only the medial aspect of the second toe was involved and only superficially. The removed hairs were of the same color and texture as the mother's. Tacking sutures were inserted in the dorsal aspects of the third and fourth toes. One week later, the toes showed good healing in proper alignment (Figure 2). The sutures were removed at this time and on subsequent evaluation there was seen to be complete healing.

Discussion

Hair wrapping of a digit is uncommon and generally not well-known to the pediatrician or emergency room physician who usually sees such a patient initially. It has been confused with infection, trauma, congenital bands and other related problems. Congenital bands especially may be confused with this clinical entity since they also present as linear, well demarcated, constricting areas around an extremity. Differentiation is not difficult if the following points are considered. Congenital bands occur intrauterine and are present at birth; however, hair wrapping is acquired and is not present at birth. In congenital bands no constricting agent is found, while in toe wrapping a hair or thread is always found. Congenital bands frequently occur on the legs as well as the digits; however, this has not been reported with hair wrapping. The treatment for hair wrapping is simple removal of the constricting agent, whereas congenital bands require serial Z plasty procedures for correction.

Figure 2.—(Case 2) Toe tip stabilized with 5-0 Nylon suture showing good alignment.

The first cases of hair strangulating an appendage were reported by Alpert and associates in 1965;[1] they described the qualities of hair that make it a particularly efficient constricting agent. Curran[2] reported an additional case in 1966 and emphasized the importance of differentiating this problem from other conditions such as infection. The term "toe tourniquet syndrome" was introduced by Quinn[3] in 1971 when he reported five cases and implicated leotard-type clothing as important in the cause of this condition. The importance of removing all loops of the strangulating hair or thread and a procedure for successfully accomplishing this was reported by Kerry and Chapman[4] in 1973; however, an additional step to prevent rotation of the unstable tip of the toe should probably be incorporated. The incidence of tip rotation is unknown but this problem certainly does occur and must be considered especially when the soft tissue defect extends to the bone. Placing a single small suture, applying steristrips or even splinting the toe for three to four days would probably prevent this complication.

Summary

Two cases of infants with partial amputation of the toe secondary to hair strangulation are presented. Although the constricting hair was successfully removed from the first patient and the toe healed satisfactorily, rotation of the tip caused the nail to impinge upon the adjacent toe. In the second patient a single tacking suture was used to stabilize the distal tip and rotation did not occur. The problem of tip rotation could lead to discomfort or disability and should be prevented by stabilization of the toe-tip after removal of the constricting hair.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Peer Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Peer Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Peer Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Treatment for Thinning Hair in Women

QUESTION:

Are injections of systemic steroids and Antuitrin S® (chorionic gonadotropin) accepted medical practice in the treatment of thinning hair in 25- to 35-year-old women? (Asked by San Diego Foundation for Medical Care)

OPINION:

In the opinion of the Advisory Panels on Dermatology and Internal Medicine, use of Antuitrin S® (chorionic gonadotropin) is not accepted medical practice for the treatment of thinning hair in young women. Low doses of corticosteroids (oral, topical and intralesional administration were mentioned) are sometimes used in the management of patients with alopecia areata. Opinion is divided as to the effectiveness of this course, but there is no preferred treatment for the condition.

Thermograms for Vascular Disease

QUESTION:

Are thermograms considered accepted medical practice for the diagnosis of vascular disease, or are they experimental? (Asked by the Medical Care Foundation of Sacramento)

OPINION:

In the opinion of the Advisory Panels on General Surgery, Radiology and Internal Medicine, opinion is divided as to whether thermograms are accepted or experimental in the diagnosis and evaluation of vascular disease.

Many respondents agreed that thermograms may occasionally provide information which is useful in a specific case, but more accepted methods of obtaining the same information would make their routine use seem inadvisable.

Occasions for thermograms might include preoperative or postoperative evaluation in cases of patients in whom sympathectomy or arterial reconstruction is done, or to establish a diagnosis of Raynaud's disease.

Vabra® Aspirator

QUESTION:

(1) Is use of the Vabra® Aspirator (vacuum curette aspirator) to perform a diagnostic dilatation and curettage (D & C) in the office without anesthesia considered accepted medical practice? (2) Is this technique safe and capable of producing results which correlate well with those obtained via the conventional approach? (Asked by Blue Shield of California)

OPINION:

In the opinion of the Advisory Panels on Obstetrics and Gynecology, and General and Family Practice, use of a vacuum curette aspirator, such as the Vabra® Aspirator, is an accepted safe medical practice.

However, curettage with this device is useful only as a screening procedure comparable to endometrial biopsy—not as a substitute for a dilation and curettage.

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 23 recognized specialities of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

DIAGNOSTIC PARASITOLOGY—Clinical Laboratory Manual—Lynne Shore Garcia, AB, MT(ASCP), Department of Pathology, Harbor General Hospital, Torrance, California; and Lawrence R. Ash, MA, PhD, Division of Epidemiology, School of Public Health, University of California, Los Angeles. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, MO (63103), 1975. 112 pages, 71 illustrations, $7.50.

Diagnosis of parasitic infestations depends largely upon the ability of the laboratory to demonstrate the pathogens in properly collected specimens. Because most technologists have very little experience with parasitologic procedures, many patients go undiagnosed in spite of a series of costly repeated examinations.

This manual should be useful to laboratorians who are interested in improving their diagnostic abilities. The authors have compiled an outline of simple, practical procedures that can be performed in almost any microbiology laboratory. The entire text is filled with many useful hints, obviously gained from the authors' broad experience in diagnostic parasitology. The methods are described in a simple, step-by-step outline format which is well-organized and easy to follow. A series of charts outline the diagnostic features of most common parasites, providing a quick reference for identifying the parasite once it is found. Additional chapters deal with methods for culturing amoeba, preservation of specimens for teaching purposes and a list of serologic procedures that are available.

This little manual should be a valuable reference for technologists working in very primitive as well as extremely sophisticated parasitology laboratories. There is useful information for everyone with an interest in this area of medicine.

A. L. BARRY, PH D

* * *

A TEXTBOOK OF RADIOLOGY—Second Edition—Edited by David Sutton, MD, FRCP, FFR, MCAR(Hon.), Director, Radiological Department, St. Mary's Hospital, London, Consultant Radiologist, Maida Vale Hospital, London, Teacher in Radiology, St. Mary's Hospital Medical School, University of London, and Institute of Neurology, University of London; Assisted by Ronald G. Grainger, MD, FRCP, DMRD, FFR, Consultant Radiologist to United Sheffield Hospitals, Consultant Radiologist in Charge, Northern General Hospital, Sheffield. Longman Inc., Churchill Livingstone-Medical Division, 72 Fifth Avenue, New York City (10011), 1975. 1,376 pages, $79.50.

This massive (weighing almost eight pounds) single volume general radiology textbook makes a better attempt than many others available to give more than a brief overview of the many facets of general radiology today. It is divided into seven parts: bones and joints; the chest; the cardiovascular system; the gastrointestinal tract and abdomen; the urogenital tracts; ears, nose and throat, eyes, teeth, soft tissues, scanning; the central nervous system. These divisions each have at least two contributors. There are some useful appendices following the text: centers of ossification, contrast media, and vascular rings and anomalies of the aortic arch. The index is rather well organized and subjects are fairly easy to find. References and suggestions for further reading are, however, extremely limited when one considers the scope of the subject material. As suggested by the great weight of the book, one of its major drawbacks is its sheer size. While to some, carrying about such a heavy volume might be good exercise, the volume already in our department library and the volume available for review are already showing signs of structural damage to the spine of the book. One would hope that the editor would opt for two volumes in the next edition as is already done in many radiology and non-radiology textbooks.

The quality of radiographic reproductions is somewhat spotty with probably fewer being suboptimal than satisfactory. One is struck by the excellence of the line drawings which are extremely helpful and are used throughout the book for illustration. Helpful also are the many tables which supplement the text such as those in differential diagnosis, chemical values and radiographic findings in various diseases. The text reads quite easily and, except for a few descriptive terms and phrases in common usage in Great Britain but not in the United States, the text is easily understood by any American reader.

The discussion about adverse reactions to contrast media (pp 876-878), I believe, deserves special criticism. Most uroradiologists in this country would decry the use of premedication as described in this section. Some would even consider anxiety as possibly playing a role in reactions to contrast media, a viewpoint not even mentioned.

Several other deficiencies are obvious: (1) no discussion of abdominal ultrasound except as it is used in obstetrics and gynecology, (2) very brief discussion of pharmacoangiography and no demonstration of its use in bleeding cases, (3) no discussion of radiologic lung biopsy techniques although a renal cyst aspiration is discussed briefly.

Despite the book's shortcomings and deficiencies, it apparently does fulfill its author's announced objective, that is, to provide a comprehensive single volume textbook for advanced trainees in radiology. I, for one, am less certain that accomplishing such an objective is possible.

ANTHONY G. PECK, MD

* * *

ATLAS OF ANATOMY OF THE HAND—Johan M. F. Landsmeer, Professor of Anatomy and Embryology, University of Leiden. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 349 pages $55.00.

Dr. Landsmeer, the author of this work, is a distinguished anatomist and ardent student of the anatomical refinements of the hand. This 349-page text documents his extensive anatomical research.

The book has, for the most part, a format of serial slides which are transverse and sagittal, with accompanying descriptive detail and analytical remarks. It would be extremely helpful to have many more labels for the innumerable photographs to identify structures discussed in the descriptive matter relating to them. Moreover, the language of the text is, in many parts, rather cumbersome and difficult to follow.

The *Atlas of Anatomy of the Hand* is a valuable reference for academic anatomists. Unfortunately, its method of presenting material is such that the work is not of practical value to average physicians diagnosing or treating disorders of hands. It is best suited to a reference library dealing with the hand.

EUGENE S. KILGORE, JR, MD

in memoriam

Babbitt, Lawrence H., San Diego. Died July 25, 1976 in San Diego, aged 44. Graduate of the University of California at Los Angeles, School of Medicine, 1965. Licensed in California in 1966. Dr. Babbitt was a member of the San Diego County Medical Society.

Elliott, Henry Wood, Santa Ana. Died August 1, 1976 in Santa Ana of heart disease, aged 56. Graduate of the University of California Medical School, Berkeley-San Francisco, 1953. Licensed in California in 1955. Dr. Elliott was a member of the Orange County Medical Association.

Fulkerson, Charles Ronald, Oakdale. Died July 4, 1976 in Oakdale, aged 65. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1936. Licensed in California in 1936. Dr. Fulkerson was a member of the Stanislaus County Medical Society.

Geier, Frederick M., Richmond. Died August 20, 1976 in Walnut Creek of injuries received in a biking accident, aged 60. Graduate of the University of California Medical School, Berkeley-San Francisco, 1945. Licensed in California in 1945. Dr. Geier was a member of the Alameda-Contra Costa Medical Association.

Graybill, Glen Arthur, Barstow. Died August 20, 1976 in Loma Linda, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1938. Licensed in California in 1938. Dr. Graybill was a member of the San Bernardino County Medical Society.

Haverback, Bernard J., North Hollywood. Died July 28, 1976 in North Hollywood of an embolism, aged 50. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1950. Licensed in California in 1953. Dr. Haverback was a member of the Los Angeles County Medical Association.

Marco, Joseph, Los Angeles. Died May 15, 1976 in Los Angeles of acute myocardial infarction, aged 69. Graduate of the George Washington University School of Medicine, Washington, DC, 1933. Licensed in California in 1937. Dr. Marco was a member of the Los Angeles County Medical Association.

Mattingly, Robert Andrew, jr., Redwood City. Died August 20, 1976 in Redwood City, aged 53. Graduate of the George Washington University School of Medicine, Washington, DC, 1946. Licensed in California in 1956. Dr. Mattingly was a member of the San Mateo County Medical Society.

Miller, Albert George, San Mateo. Died August 10, 1976 of heart disease, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1936. Licensed in California in 1936. Dr. Miller was a past president of the California Medical Association and of the San Mateo County Medical Society, and a retired member of the San Mateo County Medical Society.

Miller, Donald Glenn, Glendale. Died July 28, 1976, aged 61. Graduate of Boston University School of Medicine, 1940. Licensed in California in 1946. Dr. Miller was a member of the Los Angeles County Medical Association.

Nethery, Robert Dale, Glendale. Died July 16, 1976 in Covina of recurrent cerebrovascular accidents, aged 67. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1939. Dr. Nethery was a member of the Los Angeles County Medical Association.

Rago, Marco R., Los Angeles. Died July 12, 1976 of heart disease, aged 61. Graduate of the Creighton University School of Medicine, Omaha, 1941. Licensed in California in 1942. Dr. Rago was a member of the Los Angeles County Medical Association.

Roney, James Givens, jr., Washington, DC. Died August 23, 1976 in Washington, aged 57. Graduate of Marquette University School of Medicine, 1948. Licensed in California in 1949. Dr. Roney was a member of the San Mateo County Medical Society.

Stadfield, Clayton G., Los Angeles. Died November 13, 1975 in Hemet of heart disease, aged 89. Graduate of the College of Physicians and Surgeons, Los Angeles, 1910. Licensed in California in 1910. Dr. Stadfield was a member of the Los Angeles County Medical Association.

Webster, Bertha E., Modesto. Died August 19, 1976 in Modesto, aged 62. Graduate of Hahnemann Medical College and Hospital in Philadelphia, 1955. Licensed in California in 1956. Dr. Webster was a member of the Stanislaus County Medical Society.

Weill, Charles G., San Francisco. Died July 27, 1976 in San Francisco of cerebrovascular accident, aged 65. Graduate of Université de Lyon Faculté de Médecine et de Pharmacie, 1948. Licensed in California in 1953. Dr. Weill was a member of the San Francisco Medical Society.

Wilcox, Marvin Robert, Modesto. Died August 20, 1976 in Modesto, aged 43. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1959. Licensed in California in 1960. Dr. Wilcox was a member of the Stanislaus County Medical Society.

Zeman, Edward W., Riverside. Died November 15, 1975 of carcinoma of the rectum, aged 64. Graduate of the University of Nebraska College of Medicine, Omaha, 1936. Licensed in California in 1946. Dr. Zeman was a member of the Riverside County Medical Association.

Full meeting schedule in December issue of The Western Journal of Medicine

106th Annual Session

March 4-9, 1977 • Disneyland Hotel, Anaheim

PLAN TO ATTEND

PROGRAMS

- Lung cancer
- Ophthalmic oncology
- Allergic lung disease
- Salivary gland tumors
- Nuclear medicine in cardiovascular disease
- Pulmonary intensive care medicine
- Surgical infections and antibiotics
- Environmental pathology
- Primary care and occupational medicine
- Pediatric infectious disease
- OB topics: estrogens; home deliveries
- Regionalization of perinatal care
- CAT scanning
- Urology and endocrinology
- Herpes simplex
- Chronic low back pain
- Controversies in psychiatric treatment
- Psychopharmacology
- The medical family in crisis
- Health instruction in public schools

AFFILIATED MEETINGS

- American Cancer Society, California Division
- California Association of Ophthalmology
- California Association of Neurological Surgeons
- California Section of the American College of Obstetricians and Gynecologists
- California Society for the Treatment of Alcoholism and Other Drug Dependencies
- California Society of Allergy and Clinical Immunology
- California Tumor Tissue Registry
- California District, American Academy of Pediatrics
- California Society of Physical Medicine and Rehabilitation

MORE THAN ONE HUNDRED SCIENTIFIC AND TECHNICAL EXHIBITS

47th Annual Convention—California Medical Association Auxiliary

CALIFORNIA MEDICAL ASSOCIATION HOUSE OF DELEGATES

In vitro susceptibility updated and still virtually unchanged

Schering

A five-year history of pathogen susceptibility to Garamycin® (gentamicin sulfate)—1971-1975

	1971	1972	1973	1974	1975
Gram-Negative Susceptibility No. of Patient Isolates	98% 89,317	97% 113,473	97% 127,763	97% 150,094	97% 193,626
Escherichia coli	99%	99%	99%	99%	99%
Proteus species, indole-negative	98%	99%	99%	99%	99%
Proteus species, indole-positive	97%	96%	94%	94%	92%
Pseudomonas aeruginosa	96%	96%	95%	94%	95%
Klebsiella-Enterobacter-Serratia	99%	98%	99%	99%	98%
Staphylococcal Susceptibility No. of Patient Isolates	97% 6,995	98% 11,109	98% 12,225	99% 18,352	99% 28,130
Staphylococcus aureus	97%	98%	98%	99%	99%
Staphylococcus epidermidis	97%	97%	98%	98%	98%

Source: PMR Bacteriologic Reports—1971-1975
These *in vitro* data are based on results obtained from a nationwide panel of 180 acute-care hospitals of 100 beds or more. All hospitals in the audit used the Kirby-Bauer method of disc sensitivity. Data are presented in unweighted form.

***In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.**

See *Clinical Considerations* section which follows...

Garamycin® I.M./I.V.
gentamicin sulfate injectable
80mg/2ml.
40 mg/ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin

The seven major gram-negative pathogens and *Staphylococci* remain highly susceptible...

Schering

Of the seven major gram-negative pathogens encountered in the hospital, 97 per cent remained sensitive to Garamycin *in vitro* over a five-year period; 99 per cent of *Staphylococci* remained sensitive.

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate, U.S.P. equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY **Safety for use in pregnancy has not been established.**

INDICATIONS GARAMYCIN Injectable is indicated with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms.

Pseudomonas aeruginosa, Proteus species (indole positive and indole negative), *Escherichia coli* and *Klebsiella Enterobacter Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion, there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the seventy of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium, splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura, fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema, nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

Patients with normal renal function

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water, in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of one to two hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

011

JUNE 1975
AHFS Category 8:12:28

For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin® I.M./I.V.
gentamicin sulfate 80mg./2ml.
injectable
40 mg./ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin

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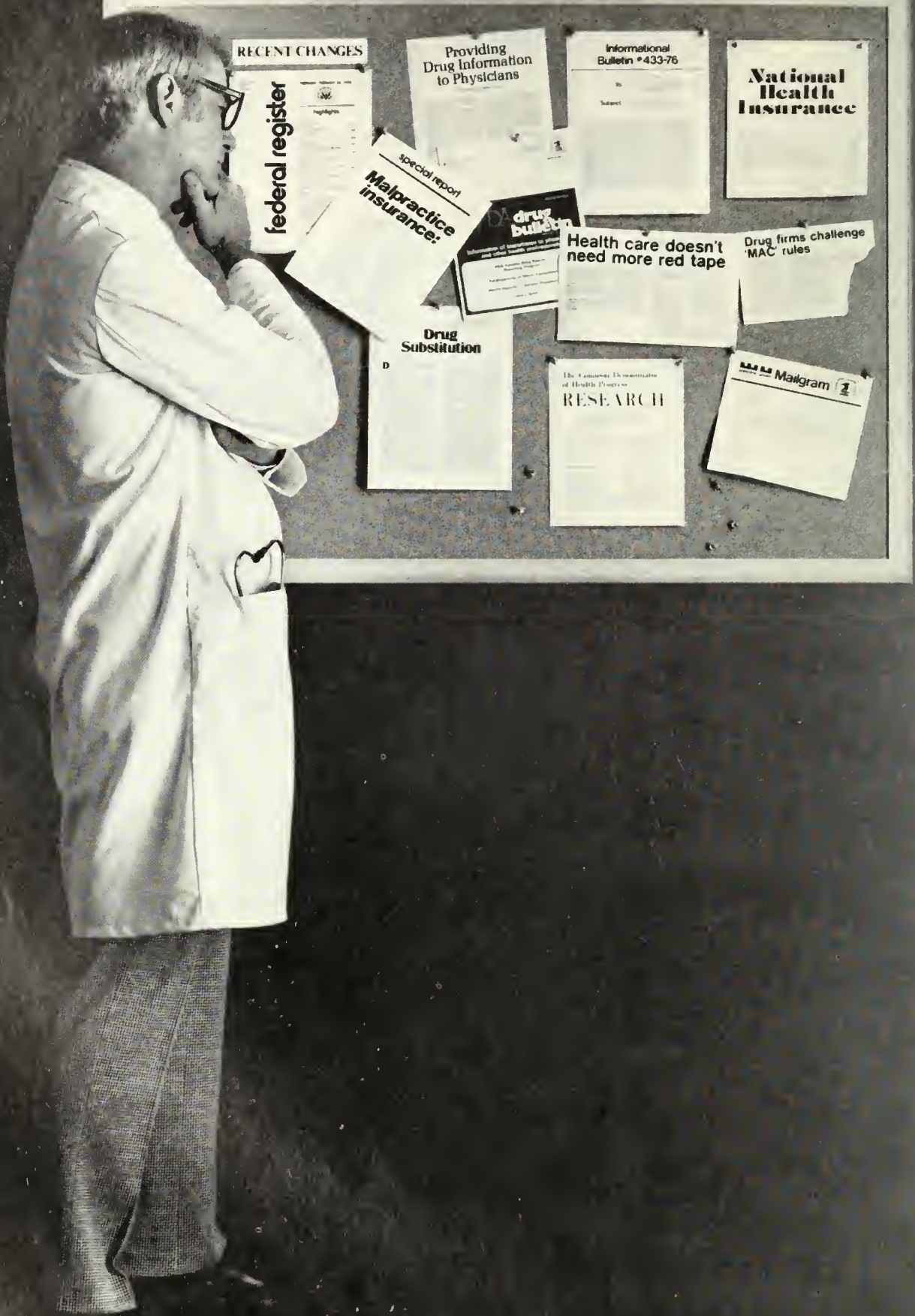
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Informational Bulletin #433-76
National Health Insurance
special report
Malpractice insurance:
drug bulletin
Health care doesn't need more red tape
Drug firms challenge 'MAC' rules
Drug Substitution
RESEARCH
Mailgram

THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005

Live a little history while you learn a lot of new medicine

American Medical Association's 30th Clinical Convention • Scientific Program
December 4-7, 1976/Philadelphia Civic Center, Philadelphia, Pa.

AMA's 30th Clinical Convention • December 4-7, 1976 • Philadelphia Civic Center

Please print and return to:

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535 North Dearborn Street
Chicago, Illinois 60610

General Registration

_____ AMA members and their guests: no fee
_____ Non-member physicians: $35
_____ Guests of non-members: $10 per person
_____ Medical students, interns, residents, Canadian, and foreign physicians: no fee

Does not include CME Course, Sessions, or Luncheons Fees.

I am a member of the AMA through the following State Medical Association or government service

_____.

If not, I have added $35 non-member fee to my course registration remittance of $_____, which is enclosed in the form of a check or money order payable to the American Medical Association. I understand payment must accompany my choice of course(s) on this registration coupon.

Confirmation of my selection(s) will be mailed to me according to the deadlines itemized. Please send AMA's Philadelphia Clinical Convention Brochure ☐.

Name _____

Office Address _____

City/State/Zip _____

Office Phone No _____

Course Code	Credit Hours	Fees	Number of Preferences Sat.	Sun.	Mon.	Tue.
S-1.	5	$ 50	___			
S-2.	6	60	___			
S-3.	6	60	___			
S-4	6	60	___			
S-5.	3	30	___			
S-6.	3	30	___			
S-7.	5	50	___			
S-8.	3	30	___			
S-9	3	30	___			
S-10	3	30	___			
S-11.	11	130		___		
S-12.	6	60		___		
S-13.	6	60		___		
S-14.	6	60		___		
S-15.	6	60		___		
S-16.	6	60		___		
S-17.	3	30			___	
S-18.	3	30			___	
S-19.	3	30			___	
S-20.	3	30			___	
S-21.	3	30			___	
S-22.	3	30			___	
S-23.	12	120			___	___
S-24.	6	60			___	
S-25.	6	60			___	
S-26.	3	30				___
S-27.	3	30				___
S-28.	3	30				___
S-29.	3	30				___
S-30.	3	30				___
S-31.	3	30				___
S-32.	6	60				___
S-33.	6	60				___
S-34.	6	60				___
S-35.	6	60				___
S-36.	6	60				___
S-37.	5	50				___
S-38.	3	30				___
~~S-39.~~	~~3~~	~~30~~				___
S-40.	3	30				___
S-41	3	30				___
S-42.	3	30				___
S-43.	5	50				___
S-44	3	30				___
~~S-45.~~	~~3~~	~~30~~				___
S-46.	3	30				___

Add $35 if Non-AMA Member ..... _____

TOTAL ..... _____

Special Note • In addition to the postgraduate courses outlined here, the Oct. 11, 1976, **JAMA** Convention Issue contains 9 general sessions, 16 luncheon sessions, and 32 "Meet the Professor" meetings available to you. The AMA's Philadelphia Clinical Convention Brochure also contains this information. All inquiries should be directed to the **AMA Department of Meeting Services, 535 N. Dearborn St., Chicago, IL 60610** and/or direct phone inquiries to: **AMA Department of Meeting Services at (312) 751-6187.**

A CME program tailored to your needs • The primary purpose of the AMA Clinical program is to provide you with a broad-based, multidisciplinary learning experience which is usually not available in specialty society continuing medical education (CME) programs. For this purpose, the scientific program features an exceptionally large and broad selection of Category 1 postgraduate courses which provide credits toward the AMA Physician's Recognition Award. In fact, the scientific program is the largest ever offered at an AMA Clinical Convention.

In Category 1, you can choose from 46 postgraduate courses, 9 general sessions, telecourses, living teaching demonstrations, and conducted exhibit rounds. In addition, Category 2 credits can be obtained by paid attendance at 16 luncheon and 32 "Meet the Professor" sessions.

The Bicentennial City • It is particularly appropriate in this Bicentennial Year that Philadelphia be the site of AMA's 30th Clinical Convention. Because Philadelphia is not only the birthplace of our Nation, but it can also lay legitimate claim to being the cradle of American medicine. It is the site of the first hospital, the first medical school, and the home of many famous American Colonial physicians, such as Benjamin Rush, John Shippen, and John Morgan.

In your off hours, you can step back into history with visits to Independence Hall, the new Liberty Bell Pavilion, Betsy Ross' House, the Franklin Institute, and many other historical sites. For all of its historical significance, Philadelphia is as modern and sophisticated a city as there is. There's a multitude of superb restaurants to delight the gourmet, including the Old Original Bookbinder's.

Plan Now for Your CME in Philadelphia • Use the coupon to register now for the postgraduate courses of your choice. The complete selection and full descriptions of the over 103 CME events will be available in the October 11, 1976, Clinical Convention Issue of the **Journal of the American Medical Association (JAMA).** You may also check the coupon box to receive the AMA's Philadelphia Clinical Convention Brochure which has material similar to the **JAMA** Convention Issue. After filling in information, send this coupon to the AMA with your accompanying check or money order. Advance registration requests must be received by October 29, 1976. Course tickets and registration materials will be sent to you on November 12, 1976. All tickets requested after that deadline date will be held for pickup at the Postgraduate Registration Desk in the Philadelphia Civic Center.

If the minimum course registration is not attained for your first choice, or if the course is full, one of your alternate choices will be substituted. It is best to register early because the class sizes are limited. All medical students, interns, and residents are entitled to a 50% discount on postgraduate course fees ($10 per Category 1 credit hour is standard rate).

Postgraduate Courses

Saturday, Dec. 4, 1976

7:30 AM-Noon (5 hours: $50)
- *S-1. Basic Life Support (Cardiopulmonary Resuscitation – CPR)

9:00 AM-5:30 PM (6 hours: $60)
- S-2. Practice Management Seminar
- S-3. Writing for Scientific Journals
- *S-4. Nutrition: Parenteral & Alimentary

9:00 AM-Noon (3 hours: $30 each)
- *S-5. Basic Electrocardiography
- S-6. Evaluation of the Dizzy Patient

1:00-5:30 PM (5 hours: $50)
- S-7. Basic Life Support (CPR)

2:30-5:30 PM (3 hours: $30 each)
- S-8. Hematologic Disorders in Children
- S-9. The Eye & Office Practice
- S-10. Coronary Artery Disease: Medical vs Surgical Therapy

Sat., Dec. 4 & Sun., Dec. 5

9:00 AM-5:30 PM & 9:00 AM-Noon (11 hours: $110, plus $20 lab fee = $130)
- S-11. Public Speaking Seminar

9:00 AM-Noon & 9:00 AM-Noon (6 hours: $60 each)
- *S-12. Fluid & Electrolyte Therapy
- S-13. Diseases of the Bowel
- S-14. Arthritis Update: Medical & Surgical Management

2:30-5:30 PM & 2:30-5:30 PM (6 hours: $60 each)
- *S-15. Management of Diabetes Mellitus
- S-16. Hypertension

Sunday, Dec. 5, 1976

9:00 AM-Noon (3 hours: $30 each)
- S-17. Diagnosis & Treatment of Fractures of the Upper Extremities
- *S-18. Advanced Electrocardiography
- S-19. Emergency Medicine

2:30-5:30 PM (3 hours: $30 each)
- *S-20. Pulmonary Function & Blood Gases
- S-21. Behavioral Problems Involving Children & Adolescents
- S-22. Recent Advances in Cancer Surgery

Sun., Dec. 5 & Mon., Dec. 6

7:30 AM-5:30 PM & 7:30 AM-Noon (12 hours: $120)
- S-23. Advanced Life Support (CPR)

9:00 AM-Noon & 9:00 AM-Noon (6 hours: $60)
- S-24. Jaundice: Diagnosis, Treatment & Management

2:30-5:30 PM & 9:00 AM-Noon (6 hours: $60)
- S-25. Everything You Want to Know About New Diagnostic Techniques: Scoping, Scanning, & Angiography

Monday, Dec. 6, 1976

9:00 AM-Noon (3 hours: $30 each)
- S-26. Diagnosis & Treatment of Fractures of the Lower Extremities
- S-27. Neonatology
- S-28. Current Controversies in Gynecology

2:30-5:30 PM (3 hours: $30 each)
- S-29. Basic Electrocardiography
- S-30. Pulmonary Function & Blood Gases
- *S-31. Complications of Psychotropic Drugs

Mon., Dec. 6 & Tues., Dec. 7

9:00 AM-Noon & 9:00 AM-Noon (6 hours: $60 each)
- S-32. Immunology 1976
- S-33. Thromboembolism: Prevention, Diagnosis, & Treatment

2:30-5:30 PM & 2:30-5:30 PM (6 hours: $60 each)
- S-34. Fluid & Electrolyte Therapy
- S-35. Nutrition: Parenteral & Alimentary
- S-36. Management of Diabetes Mellitus

Tuesday, Dec. 7, 1976

7:30 AM-Noon (5 hours: $50)
- S-37. Basic Life Support (CPR)

9:00 AM-Noon (3 hours: $30 each)
- S-38. Diagnosis & Treatment of Fractures in Children
- ~~*S-39. Dermatology for the Nondermatologist~~
- S-40. Allergic Emergencies
- S-41. Medical Problems in Long-Term Care
- S-42. Acute Hand Problems

1:00-5:30 PM (5 hours: $50)
- S-43. Basic Life Support (CPR)

2:30-5:30 PM (3 hours: $30 each)
- S-44. Advanced Electrocardiography
- ~~S-45. Dermatology for the Nondermatologist~~
- S-46. Complications of Psychotropic Drugs

*Course repeated. See course list for dates & times.

AMA HOUSING BUREAU * Suite 1420
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1617 John F. Kennedy Boulevard
Philadelphia, Pennsylvania 19103

30th AMA Clinical Convention
December 4-7, 1976 • Philadelphia, Pa

Housing Form

Key #	Hotel/Motel	Single	Double	Twin	Suite
1.	Bellevue Stratford	$27.00-40.00	$34.00-47.00	$34.00-47.00	$ 60.00-105.00 (1 Bedroom) 107.00-152.00 (2 Bedrooms
2.	Hilton of Philadelphia	30.00-40.00	40.00-50.00	40.00-50.00	110.00-190.00 (1 Bedroom) 160.00-250 00 (2 Bedrooms
3.	**Holiday Inn — Center City**	**CO-HEADQUARTERS HOTEL**		**NO ROOMS AVAILABLE**	
4.	Penn Center Inn	25.00-27.00	30.00-32.00	30.00-32.00	60.00 (1 Bedroom) 90.00 (2 Bedrooms)
5.	**Philadelphia Sheraton**	**HEADQUARTERS HOTEL**		**NO ROOMS AVAILABLE**	
6.	University City-Holiday Inn	29.00	36.00	36.00	95.00-105.00 (1 Bedroom)
7.	Warwick Hotel	32.00-38.00	38.00-44.00	38.00-44.00	75.00-100.00 (1 Bedroom) 100.00-150.00 (2 Bedrooms

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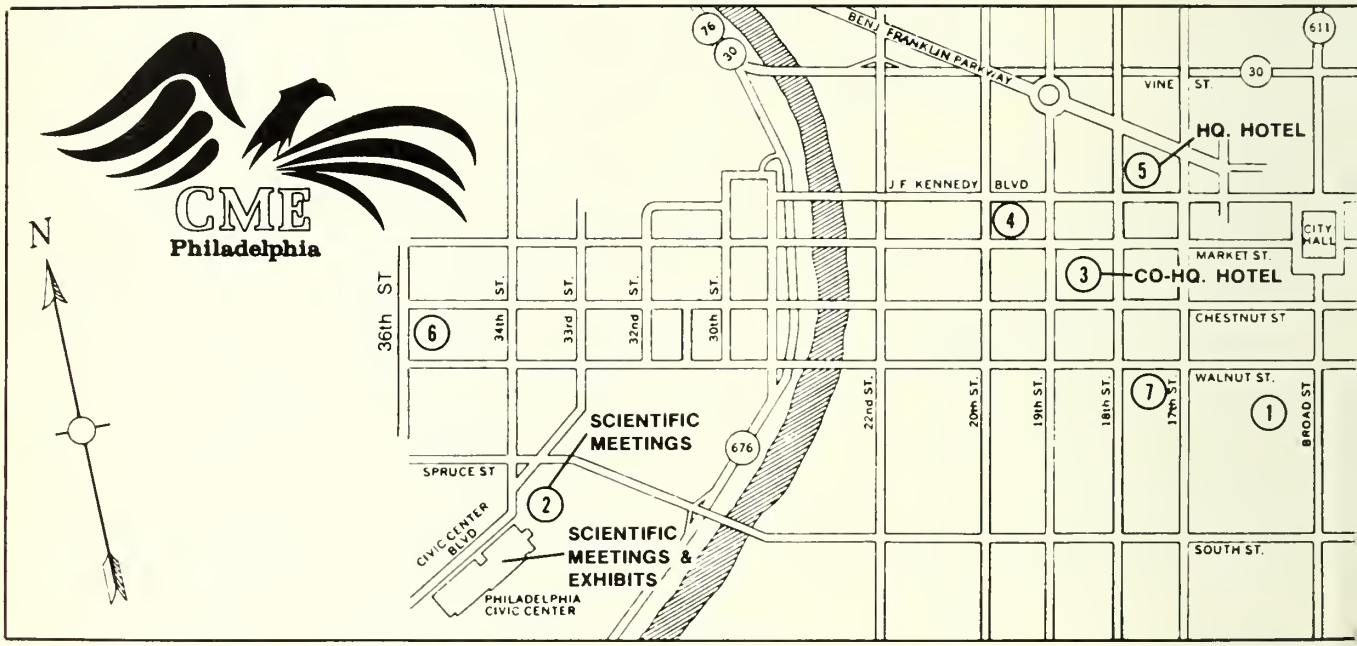

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Please add 6% for the House Occupancy Tax; if your rate requested is not available the next highest rate will be assigned. **DO NOT** send your request directly to the hotel it will only delay your confirmation. Kindly make all necessary changes and cancellations directly with the Housing Bureau in Philadelphia, and be sure and specify your time of arrival, as well as the date. If you are an Industrial Exhibitor, please specify your firm's name and the list of all the occupants for all the rooms that you are reserving

CONFIRMATIONS WILL BE MAILED UP TO NOVEMBER 12, 1976.

Room will be occupied by

Name _____
(Please print or type.)

Firm _____

Address _____

City/State/Zip Code _____

Office Phone Number ( ) _____ - _____

Additional Occupants (List ages of children, if any)

_____

Arrival Date _____ at _____ AM, PM, Departure Date _____

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

INTERNIST board certified or eligible, CARDIOLOGY preferred as sub-specialty, to join partnership of well established group of internists. Reply with C.V. to R. J. Bartlett, MD, 909 Hyde Street, Suite 125, San Francisco, CA 94109.

GENERAL SURGEON—with Orthopedic experience. 10 man group practice. 110 bed hospital. New clinic building being erected. Midwestern city of U.S.A. of 8,000. Good trade area. Salary over $40,000 per year, early partnership. Write Box 9478, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIANS (1 or 2) wanted to complete full group care in large, multi-specialty group in the East Bay area of San Francisco. Adjacent to large pedodontal group. Two OB-GYN men in group. Additional 3,500 sq. ft. under construction in complex. Will build to suit. Reply to Danville Medical Group, 318 Diablo Rd., Danville, CA 94526; (415) 837-4202.

FAMILY PRACTITIONER/GP—Immediate opening in San Diego with growing multi-specialty group. Extremely attractive salary with generous perquisites. Send C.V./Résumé to Corey Marco, MD, P.O. Box 14253, San Diego, CA 92114.

PEDIATRICIAN—Rapidly growing multi-specialty group in San Diego seeks additional pediatrician for its staff. Immediate opening, no overhead, extremely attractive salary with generous fringe benefits. Send C.V./Résumé to Medical Director, P.O. Box 14253, San Diego, CA 92114.

CALIFORNIA—BOARD CERTIFIED, ANESTHESIOLOGIST for Chief, Anesthesia Section needed at VA Hospital, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position will be available in early December. Salary dependent on experience and qualifications. Contact: Byron V. Whitney, MD, FACS, Chief, Surgical Service, VA Hospital, Livermore, CA 94550; Tel: (415) 447-2560, ext. 213.

BOARD CERTIFIED PHYSICIAN—Associate Director for growing national professional association. Interest and experience in Medical Education, especially Graduate Training is essential. Competitive salary, fringe benefits. Inquire and send résumé to Executive Director, American Board of Medical Specialties, 1603 Orrington, Evanston, Illinois 60201.

UCLA SCHOOL OF MEDICINE, DEPARTMENT OF ANESTHESIOLOGY, seeks a Chairman of the Department of Anesthesiology at Kern Medical Center, its affiliate in Bakersfield, California. Board certification and California license essential. Salary open, full medical liability coverage. Interested candidates should direct inquiries or submit credentials (including curriculum vitae) to Donald F. Brayton, MD, Medical Director, Kern Medical Center, 1830 Flower Street, Bakersfield, California 93305; telephone (805) 322-3313. Both the University of California and Kern Medical Center are equal opportunity employers.

GROUP PRACTICE OPPORTUNITIES

Due to rapid growth, The Permanente Clinic, a large multi-specialty partnership located in the heart of the Pacific Northwest, has opportunities available in these specialties:

- Neurosurgery
- Obstetrics/Gynecology
- Otolaryngology
- Radiology
- Orthopedic Surgery
- Internal Medicine
- Emergency Care
- Oncology
- Neurology

The Permanente Clinic is a multi-specialty professional partnership of approximately 180 physicians which supplies the professional services for 200,000 members of the Kaiser Foundation Health Plan. Through its association with the Kaiser Foundation Health Plan, the Permanente Clinic operates seven clinics and two full-service hospitals in the Portland metropolitan area.

The Permanente Clinic offers physicians a pure medical practice, free of all practice costs and administrative problems. We offer a liberal compensation and benefit package including three weeks' vacation, one week educational leave annually, a sabbatical program, malpractice coverage, disability, health, dental and life insurance, and two excellent retirement programs. We also offer a 4½ day work week.

Portland, Oregon is a major and modern metropolitan area of one million people. Recreational facilities for fishing, hunting, skiing and water activities, as well as cultural and entertainment opportunities are superb. According to a recent study sponsored by the Environmental Protection Agency, Portland has been assessed to be the most "livable" city in the U.S.

Please send a curriculum vitae with your initial response to:

MARVIN H. GOLDBERG, MD, Area Medical Director
The Permanente Clinic
1500 S.W. First Avenue
Portland, Oregon 97201

The Permanente Clinic is an equal opportunity employer—minorities and women are encouraged to apply.

PHYSICIANS WANTED

PATHOLOGISTS: The Department of Pathology at UCLA is willing to consider applications for appointment to the Clinical Staff on a volunteer basis. Applicants should have expertise in teaching and an interest in participating in the instructional program for the Second Year Medical and Dental Students as well as Interns and Residents of the department. UCLA is an Equal Opportunity/Affirmative Action Employer. Send Curriculum Vitae to J. L. Van Lancker, MD, Department of Pathology, University of California, Los Angeles, Los Angeles, CA 90024.

FAMILY PHYSICIAN AND GENERAL SURGEON needed by small multispecialty group. Outstanding clinic and hospital. Progressive small community with family atmosphere. Liberal salary and benefits. Malpractice insurance paid. Contact R. A. Callis, McCrary-Rost Clinic, Lake City, Iowa 51449; (712) 464-3194.

EMERGENCY PHYSICIANS: Continue to live at home; supplement your income while commuting to our nationwide locations. Scheduling flexible—weekends, weekly or monthly—part-time, locum tenens or full-time. Commuting allowance, paid malpractice and state license fees; excellent remuneration. Contact Drs. Cooper, Spurgeon or Greenberg toll free 1-800-325-3982 for details.

ASSOCIATE CHIEF OF SURGERY: Full time position in county owned teaching hospital, for Board Certified general surgeon with vascular surgery experience, to assist in residency training program direction and supervision. Salary approx. $48,000/yr., incl. malpractice insurance, vacation and sick leave. Contact Buford H. Burch, MD, Chief of Surgery, Highland General Hospital, 1411 E. 31st St., Oakland, CA 94602; (415) 534-8055.

(Continued on Page 30)

ANESTHESIOLOGIST

Join two man group in new 300+ bed community hospital—Ozark Area—a paradise of recreational activities, fine pleasant community atmosphere. Desirable environmental situation. Town 65,000—Area 300,000. **Edward J. Safranek, MD, 216A North Greenwood Avenue, Fort Smith, Arkansas 72901.**

PRACTICE OPPORTUNITIES

Want wide open spaces—clean air—a good environment and excellent school system for your children? See Burns, Oregon, (County population is 8,000). Located in Eastern Oregon, this small friendly community is in need of a young family practitioner and a general surgeon. Present medical staff includes six family practitioners desirous of restricting their practice, and weekly consulting Radiologists and Pathologists from Bend, Oregon. Partnership agreement available in a 4-physician clinic. A 49-bed hospital contains newly remodeled facilities. Hunters and fishermen attracted from the entire state. Ideal opportunity in this growing community. Contact **Keith Lundberg, Executive Director, Harney County Hospital, 557 W. Washington, Burns, Oregon 97720; Phone (503) 573-7281.**

(Continued from Page 29)

PHYSICIANS WANTED

PSYCHIATRIC RESIDENCY TRAINING—Program with or without mixed psychiatry-medicine internship offered by Fresno County Department of Health in conjunction with new UCSF Medical Education Program. Dynamically oriented within outstanding innovative community mental health program. Few service requirements, much elective choice, close personal supervision, extensive didactic teaching. Opportunity for work with rural and Mexican-American populations. California license required by end of first year. Salary $14,150-$20,400, plus fringe benefits. Nondiscriminatory. Contact: George F. Solomon, MD, Clinical Professor of Psychiatry, UCSF, Director of Medical Education, Fresno County Department of Health, P.O. Box 11867, Fresno, CA 93775. Phone (209) 483-3076.

FULL-TIME ORTHOPEDIC SURGEON needed for faculty of UCLA-Antelope Valley Hospital Medical Center. Family Practice Residency Program. First-year salary, $60,000 to $70,000 with attractive fringe benefits including malpractice ins. Excellent opportunity for private practice thereafter. Smog-free area 55 miles from Los Angeles. Contact Michael Drennan, 1600 West Avenue J, Lancaster, CA 93534; (805) 948-4577, Ex. 455.

GENERAL PRACTITIONER, FAMILY PRACTITIONER, AND OPHTHALMOLOGIST—to join a group based in a beautiful setting, near the U.S. Air Force Academy, specializing in rural health care. Salary is negotiable with generous fringe benefits. Contact David L. Trent, MD, Rampart Clinic, P.O. Box 366, Monument, CO 80132. (303) 481-2241.

PRIMARY CARE PHYSICIAN, WEEKEND COVERAGE, hospital-based, some week nights, excellent salary ($3,000-$4,000 per month), no overhead, challenging opportunity, immediate placement, send c.v. to Barbara Rice, Central Orange County Medical Group, 450 N. Roxbury Drive, Suite 604, Beverly Hills, CA 90210.

HOSPITAL DIRECTOR

Fulfill your ambitions as our Director of Clinical Psychiatric Services.

This is a rare opportunity to coordinate all of the clinical psychiatric services of a 45-bed residential short-term psychiatric treatment unit. We are located in a scenic section of Idaho, and serve the 10 northernmost counties in the state.

You will be responsible for directing all clinical activities, including establishing policies and procedures, maintaining quality levels, and supervising a bright, progressive staff. To qualify you'll need an M.D. degree with Idaho license, plus at least 2 years of related supervisory experience. You should be certified by the American Board of Psychiatry & Neurology, or eligible for examination, and must have a good knowledge of administrative practices of local, state, and federal health agencies.

We offer excellent starting salary of $28,032 to $38,400 per year, generous fringe benefits, and a magnificent location for an outdoor sports enthusiast. For confidential consideration, please call or write: Judy Aitken, Department of Health & Welfare, Statehouse, Boise, Idaho 83720, or telephone (208) 384-2825.

We are an equal opportunity employer m/f.

APPALACHIAN REGIONAL HOSPITALS

Malpractice Insurance Problems?—You are Needed In Appalachia

A rural regional health care system located in the beautiful mountains of Eastern Kentucky, Virginia and West Virginia needs Family Practitioners, OB-GYN, Radiologists, Psychiatrists, ENT, General Surgeon, Internists and specialists in Emergency Medicine for its ten (10) hospitals and Primary Care Centers. ARH provides comprehensive health and health related services to a major segment of rural Appalachia. Excellent starting salaries and fringe benefits include malpractice insurance, four (4) weeks paid vacation, paid health insurance, and moving expenses.

Send C.V. to:

GARY J. SMOCK, Manager of Employment
Appalachian Regional Hospitals
P.O. Box 8086
Lexington, Kentucky 40503
1-606-255-4431

FAMILY PRACTITIONER AND UROLOGIST for Western Colorado eleven man multispecialty group. Established practice close to skiing, hiking, trout fishing, big game hunting and year round Hot Springs swimming pools. Modern clinic facility located next to 40 bed hospital. Contact G. Thomas Morton, MD, Glenwood Medical Associates, 1905 Blake Ave., Glenwood Springs, Colorado 81601.

FACULTY FOR EMERGENCY MEDICINE RESIDENCY PROGRAM beginning July 1976, university affiliated teaching hospital. Board Certified in Surgery, Internal Medicine or recent graduate-approved residency in Emergency Medicine. Salary competitive; malpractice insurance paid. California license necessary. Send curriculum vitae and names of three references to: William G. Malette, MD, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305. Telephone: (805) 323-7651, extension 346.

PRIMARY CARE PHYSICIANS—If you are interested in living in the Pacific Northwest, we may be able to assist you in finding the practice location best suited to your professional and personal interests in Washington State. The Clearinghouse: Community Advocates for Health Resource Development, a non-profit organization, works in collaboration with the Washington State Medical Association. Write for complete information. 1370 Stewart St., Seattle, Wash. 98109. Phone (206) 624-3272.

California
Stanford University Hospital
IMMEDIATE OPENING

There is a position available immediately for a part-time or full-time emergency physician to work in the Stanford University Emergency Department. The schedule will include both day shifts (10 hours) and night shifts (14 hours). The vacant position is for a licensed physician with appropriate training to provide direct emergency care, and to supervise intern and medical student activities.

Requirements: Board eligibility in medicine, surgery or emergency medicine is preferable. To be considered, all applicants must have at least completed post-graduate year II of medical training.

Salary commensurate with training.

Interested applicants should immediately call:

DR. MICHAEL ELIASTAM
Director of Emergency Services
(415) 497-6576

INTERNIST AND FAMILY PRACTITIONER needed to replace retiring member of Six man Medical Corporation. Small metropolitan area. Very friendly with close proximity to big Cities and beaches. Local City College and 4 year College with all social amenities and sport. 4½ day week, prepaid malpractice, on call shared by all in group. Competitive salary 1st year—full corporate stock holdership after 1st year. Full Corporate benefits immediately. Write: B. R. Ericsson, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

EXECUTIVE DIRECTOR of a community health maintenance organization: Requirements are an advanced degree in public health administration or medicine or law with considerable health-related administrative experience. Must have demonstrated competence in administering a system of health services delivery, working with a Board of Directors, and developing proposals for funding. Salary negotiable. Send résumés before Nov. 1 to R. B. Cain, Dept. of Psychiatry, U.K.M.C., Lexington, Ky. 40506.

HOSPITAL EPIDEMIOLOGIST POSITION AVAILABLE

The Los Angeles County—University of Southern California Medical Center, an equal opportunity employer, has a position available for a physician epidemiologist responsible for the organization and conduct of an infection control program within the Medical Center. Qualifications for appointment include the completion of a residency approved by the American Board of Internal Medicine or the American Board of Pediatrics, experience in public health and epidemiology, and an interest in infection control procedures. Academic qualifications should be consistent with appointment to the faculty of medicine of the University of Southern California. A valid California State Physician and Surgeon's Certificate authorized by the Board of Medical Examiners of the State of California is required. Appropriate office facilities and staff are available.

For further information contact

DR. PAUL F. WEHRLE
Chairman, Infection Control Committee
Pediatric Pavilion
1129 North State Street
Los Angeles, California 90033

Those interested should forward a current curriculum vitae and bibliography.

Salary commensurate with training and experience.

PHYSICIANS WANTED

INDUSTRIAL PHYSICIAN — wanted for large multinational corporation. Full time in the Los Angeles Area. Competitive salary, fringe benefits, malpractice insurance. California license required. Box No. 9486, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DIRECTOR OF MEDICAL SERVICES, City of Long Beach, $32,064-$39,552 Annually. Directs all medical personnel and operations for the Health Department. Additionally, directs Communicable Disease Control Program, usual public health programs, and laboratory operations. Medical services are delivered in a variety of ambulatory care clinics, neighborhood centers, and drug and alcohol facilities. Has budget in excess of one million dollars. REQUIREMENTS: Experience —background should include general medical experience as well as public health experience. Master of Public Health degree substitutable for one year public health experience. Supervisory and administrative experience highly desirable. Training—graduation from an approved medical school. Successful completion of a rotating internship in an accredited hospital. Master of Public Health degree desirable but not required. Licenses—possession of a current California Physicians and Surgeons license. A valid California driver's license. Apply by Oct. 29, 1976. Send Curriculum Vitae to Barney J. Walczak, Deputy City Manager, Personnel and Employee Relations, Room 100, City Hall, 205 W. Broadway, Long Beach, CA 90802.

RURAL PRACTICE OPPORTUNITIES THROUGHOUT THE INTERMOUNTAIN WEST. Information on communities, practices and placement assistance offered free of charge by University of Utah College of Medicine. Great area for outdoor activities, family life and medical practice. Contact Dr. R. Woolley, Department of Family and Community Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132. (801) 581-5223.

DOCTORS HOSPITAL COLUMBUS, GEORGIA

Very attractive opportunity for a practice in Internal Medicine, Neurology, Neurosurgery. New 252-bed facility in the heart of a thriving medical community. Attractive recruitment package offered. Ample office space available. For more information send C.V. to: **Paul J. Holley, General Care Corporation, 6213 Charlotte Avenue, Nashville, Tennessee 37209.**

MEDICAL EQUIPMENT WANTED

USED X-RAY—200 to 300 MA in good operating condition. Prefer fixed grid and stationary table. Must be located in central or northern California. Contact Jon Vilhauer, DVM, 6610 Mother Lode Drive, Placerville, CA 95667; (916) 622-3943.

PHYSICIAN ASSISTANTS AVAILABLE

Several qualified Primary Care and Specialist PA's available for placement in California. NCCPA certified or eligible. All available résumés forwarded on request. Contact: **Rod Moser, P.A.-C, Calif. Academy of Physician Assts., 149 Jordan Avenue, San Anselmo, CA 94960**

PHYSICIAN'S ASSISTANT

PHYSICIAN'S ASSISTANT (Stanford University graduate) trained in Primary Care, seeks position in FP/GP office or Clinic in Bay Area. Excellent experience in Pediatrics, OB/GYN, Medical trauma and Counseling. Phone—Jo Ann Chase (916) 365-4789.

RECENT GRADUATE of 2 yr Physicians Assistant program (B.S.) very interested in locating in West Coast area. Have broad medical interests. Contact Steve Davis (801) 485-5435 collect.

SITUATIONS WANTED

RADIOLOGIST, certified, excellent training and experience in all phases of diagnostic radiology, including interventional procedures, mammography, etc. U.S. graduate, able administrator, California licensed. Now in solo, fee-for-service hospital practice. Seeking same in medium-sized (75-150 bed) hospital, Northern California, Oregon, Utah, Nevada or partnership in small radiology group in scenic area of same. Desire on location interview. Available three months notice. Premier male chief technician will also relocate. Reply Box No. 9473, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICING INTERNIST (Clinical Professor of Medicine) wishes employment during January, February, March preferably in Los Angeles South Bay. Special interests are Thyroid, Diabetes and Executive Type examinations. Write: Box 9474, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PHYSICIAN—Board certified, 34, well experienced, U.S. graduate. Seeking association with stable, high quality family practice group in California coastal community. Write Box No. 9482, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ANESTHETIST—TEMPORARY OR PERMANENT—Qualified anesthetist—international service. Anesthesia Services, 440 Davis Court, No. 311, San Francisco, CA 94111 (415) 391-3339.

PULMONARY-INTERNIST, 29, University trained, AOA, P.F.T.'S, Fibroptic Bronchoscopy. Desires medium sized community with good schools. Practice type flexible. Available July, 1977. Box No. 9484, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICE FOR SALE

WELL-ESTABLISHED MONTEREY BAY AREA California practice and equipment for sale through association with ophthalmologist who will semi-retire. Full retirement in five years. Reasonable terms. Excellent opportunity. Send complete résumé and recent photograph. Write Box 9485, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

PHARMACY WANTED

PHARMACIST wishes to establish pharmacy in Clinic, Medical building, Hospital or group of Doctors who want a pharmacy with, or without partnership. Contact Allen H. Fox, 1916 Malcolm Ave., Los Angeles, CA 90025; (213) 279-1231.

VACATIONS/MEDICAL PROFESSIONALS TAX DEDUCTIBLE VACATIONS FOR MEDICAL PROFESSIONALS.

Over 500 listings of national/international meetings in the medical sciences for 1977. Send a $10 check or money order payable to Professional Calendars, P.O. Box 40083, Washington, D.C. 20016.

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INFORMATION

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MEDICAL BUILDING

SAN FERNANDO VALLEY: Lease/Sale. One-story medical building, 2,200 sq. ft., near hospital. 16 rooms, ample parking, lot 50×260 ft. With 10 percent down will take back 90 percent T.D. Payments less than rent. Previous tenant (retired) grossed over $200,000 a year. Room for several doctors. Call (213) 277-1225 or Write 1193 S. Rodeo Dr., Los Angeles, CA 90035.

OFFICE TO SHARE

SAN RAFAEL OFFICE, share up to 4 days per week. Full time nurse, equipment, treatment rooms. Dr. Carmody (415) 479-1644.

OFFICES FOR LEASE OR RENT

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

GEN. PRACTITIONER WANTED. Semi-rural Marin location. New ofcs. 20 mins. from hospital. Available for occupancy 11/1/76. Call Bill White—(415) 479-7300 days, (415) 488-9642 evenings.

CALIFORNIA—Woodland. Custom designed suite for lease in new medical-dental building across street from hospital and major medical clinic. Contact: Woodland Dental Group, 1204 Cottonwood Street, Woodland, California 95695. Phone (916) 662-5485.

OFFICE AVAILABLE

Design Your Ideal Office

Professional partnership seeks physicians interested in participating in a new condominium office building in Milpitas. Noncompetitive location on best corner site in city. Ten minutes' drive to Alexian Brothers Hospital. Sound investment opportunity for GP, FP, internist or other physician. First owner of suite can accelerate depreciation and obtain other tax benefits. Present physician to patient ratio of 1 to 5,000 in Milpitas, and 6 established dentists will refer new patients.

For details call or write:

FREDERICK SIEMON, DDS
(408) 946-0777
210 S. Main Street, Suite 2
Milpitas, CA 95035

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALCOHOLISM AND DRUG ABUSE

October 16—**Polydrug Abuse.** USC. Saturday.

CANCER

October 23—**Symposium on Endometrial Carcinoma.** St. John's Hospital, Santa Monica. Saturday. $30. Contact: James Moran, MD, 2200 Santa Monica Blvd., Santa Monica 90404.

October 29-30—**The Professional Team Approach to Cancer Health Care.** Claire Zellerbach Saroni Tumor Institute, Mt. Zion Hospital and Medical Center, at Hyatt Regency, San Francisco. Friday-Saturday. 11½ hrs. $110 for team (physician and one supportive professional); $85 for physician. Contact: Dept. of Continuing Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2401.

December 10-11—**Current Trends in Cancer Therapy.** Daniel Freeman Hospital at Marriott Hotel, Los Angeles. Friday-Saturday. $85. Contact: Donald Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hospital, P.O. Box 100, Inglewood 90306. (213) 674-7050.

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. 6 hrs. $100. Contact: CTTR, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

December 29-30—**Clinical Cancer Symposium.** USC. Wednesday-Thursday.

January 24-28—**Cancer.** STAN. Monday-Friday. $250.

MEDICINE

October 15-16—**Internal Medicine Symposium—Neurology, Psychiatry and Internal Medicine.** Southern Calif. Permanente Medical Group at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16—**Practical Applications of Cardiovascular Nuclear Medicine.** DREW at Martin Luther King Jr. General Hospital, Los Angeles. Saturday. $85. Contact: DREW or Charles K. Francis, MD, Cardiology Dept., Martin Luther King Jr. General Hospital, 12021 S. Wilmington Ave., Los Angeles 90059. (213) 639-8550.

October 16-17—**Cardiovascular Physiology.** UCSF. Saturday-Sunday.

October 18-22—**Workshops in Internal Medicine.** American College of Physicians at University of Hawaii, Honolulu. Monday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, Pa. 19104.

October 30-November 6—**Evaluation of Neoplastic Lymphatic Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

November 3—**Echocardiography.** LLU. Wednesday. 6 hrs.

November 3—**Respiratory Diseases.** Donald N. Sharp Memori Community Hospital, San Diego. Wednesday. $10 for men bers of Sharp; $20, non-members. Contact: Milo A. Youe MD, Dir., CME, Donald N. Sharp Memorial Communit Hosp., 7901 Frost St., San Diego 92123. (714) 292-2121.

November 5-6—**Cardiovascular Disease Symposium—26th Ai nual.** San Diego County Heart Association at Vacation Vi lage, San Diego. Friday-Saturday. 10 hrs. Contact: San Dieg County Heart Assn., 3640 5th Ave., P.O. Box 3625, Sa Diego 92103.

November 6-7—**Dermatologic Surgery—Skin Grafting.** See Su gery, November 6-7.

November 8-12—**Pediatric Allergy and Clinical Immunolog** UCSF. Monday-Friday.

November 10—**Hypertension.** UCSF at Hyatt on Union Squar San Francisco. Wednesday.

November 13-14—**Kidney Function.** UCSF. Saturday-Sunday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

November 27-29—**Advances in Heart Disease—1977.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

November 29-December 3—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians at Queensway Hilton Hotel, Long Beach. 27 hrs. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

December 2-3—**Respiratory Failure Workshop.** USC. Wednesday-Friday.

December 8-10—**Respiratory Failure Workshop.** USC at Canyon Hotel, Palm Springs. Wednesday-Friday.

December 11—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. $250.

January 3-June 27—**Internal Medicine Board Review Course.** UCSD at University Hospital, San Diego. Monday evenings. 75 hrs.

January 14-15—**Identification of the Fifty Common Dermatoses.** UCSF. Friday-Saturday.

January 15—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

January 17-20—**Ischemic Heart Disease Problems and Perspectives.** Univ. of Hawaii School of Medicine, American Heart Assn., Hawaii Heart Assn. at Royal Lahaina Hotel, Maui, Hawaii. Monday-Thursday. 13 hrs. $175. Contact: Hawaii Conference Services, P.O. Box 22679, Honolulu 96822.

January 21-23—**Advances and Controversies in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, MD 20014.

January 23-29—**Topics in Internal Medicine—2nd Annual.** UCSD at Town and Country Hotel, San Diego. One week.

January 24-26—**Cardiac Auscultation.** American College of Physicians at LLU. Monday-Wednesday. 18 hrs. Contact: Registrar of Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 26-28—**Advances in Neurology.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

MENTAL RETARDATION

November 3-5—**Current Aspects of Mental Retardation.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

OBSTETRICS AND GYNECOLOGY

October 23—**Symposium on Endometrial Carcinoma.** See Cancer, October 23.

October 25-26—**New Horizons in Perinatal Intensive Care—5th Annual Seminar.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. Contact: Robin J. Grant, MPH, Coord. of Cont. Ed., Harbor General Hospital, 1124 W. Carson, Torrance 90502. (213) 328-2380, ext. 1374.

October 25-29—**Ob/Gyn Review.** USC at Beverly Hilton Hotel, Beverly Hills. Monday-Friday.

October 29—**Advances in Obstetrics and Gynecology.** UCD and Northern California Ob-Gyn Society at Red Lion Motor Inn, Sacramento. Friday. Contact: UCD.

January 6-June 30—**Ob-Gyn Review.** UCLA. Thursdays.

January 13-14—**Current Concepts in Prenatal Diagnosis.** UCSD at Hilton Hotel, San Diego. Thursday-Friday.

January 14—**Infections and Septic Shock in Obstetrics and Gynecology.** California Hospital Medical Center, Los Angeles. Friday. 5½ hrs. $15. Contact: Keith P. Russell, MD, Dir., Ob-Gyn Resident Training Program, CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

January 29-February 5—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

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MY SPECIALTY (IF ANY) IS: ☐ Anesthesiology ☐ Family Practice ☐ Psychiatry ☐ Internal Medicine ☐ OB GYN ☐ Neurology ☐ Radiology ☐ Pathology ☐ Pediatrics ☐ Surgery

STATUS (CHECK ONE): ☐ Private Practice ☐ Hospital Staff ☐ Intern ☐ Resident

PEDIATRICS

October 22-23—**Nutrition in Children.** UCD and Sacramento Pediatric Society at Red Lion Motor Inn, Sacramento. Friday-Saturday. $45.

November 8-12—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 8-12.

December 4—**American Academy of Pediatrics, California Chapter I, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

January 13-16—**Ski and Study Symposium—2nd Annual.** American Academy of Pediatrics, California Chapter 2, at Mammoth Mountain. Thursday-Sunday. 14½ hrs. $125. Contact: AAP, Calif. Chapter 2, P.O. Box 2134, Inglewood 90305.

January 22-23—**Pediatric Urologic Seminar.** Children's Hospital of Los Angeles. Saturday-Sunday. Contact: H. H. Edelbrock, MD, Program Dir., CHLA, P.O. Box 85544, Los Angeles 90027.

January 28-30—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 28-30.

PSYCHIATRY

October 29-30—**Behavioral Medicine: Strategies for Health Behavior Change.** See Of Interest To All, October 29-30.

November 8-12—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

November 12-14—**Dimensions in Psychiatry-1976; from Contemporary Research to Clinical Application—3rd Annual Conference.** California Psychiatric Association at Hilton Inn, Mission Bay, San Diego. Friday-Sunday. 14 hrs. Contact: Sara J. Grossman, Assn. of Calif. Branches, APA, 2232 Carlton St., Berkeley 94704. (415) 848-5330.

December 2-5—**Treatment of Sexual Dysfunctions.** See Of Interest To All, December 2-5.

January 4-March 15—**Intensive Review of Psychiatry and Neurology.** USC. Tuesdays. 40 hrs.

January 30-February 4—**Mid-Winter Program for Psychiatrists—3rd Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

RADIOLOGY AND PATHOLOGY

October 15-17—**Radiology of the Genitourinary System.** American College of Radiology at Fairmont Hotel, San Francisco. Friday-Sunday. 15 hrs. $200 for members; $240, nonmembers. Contact: Maurine H. Trautz, Conf. Coord., ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015. (301) 654-6900.

October 16—**Practical Applications of Cardiovascular Nuclear Medicine.** See Medicine, October 16.

October 21-29—**American Society of Clinical Pathologists and College of American Pathologists.** Hilton Hotel, Los Angeles. Nine days. Contact: D. L. Gilcrest, ASCP, 2100 W. Harrison St., Chicago 60612.

October 26-29—**Symposium in Diagnostic Radiology.** UCSD at Vacation Village, San Diego. Tuesday-Friday.

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** See Cancer, December 12.

January 28-30—**Midwinter Radiological Conference—29th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Ronald W. Thompson, MD, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029.

January 28-30—**Radioimmunoassay Symposium.** UCSF. Friday-Sunday.

January 31-February 4—**Computerized Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

SURGERY AND ANESTHESIOLOGY

October 15-17—**Regional Anesthesia.** Anesthesiology Educational Foundation and Calif. Society of Anesthesiologists at Monterey. Friday-Sunday. 9½ hrs. Contact: Stuart F. Sullivan, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

October 26-November 30—**Surgical Anatomy and Surgery** USC. Tuesday evenings.

November 5-6—**Clinical Electromyography.** American Association of Electromyography and Electrodiagnosis at Sheraton Harbor Island, San Diego. Friday-Saturday. 12 hrs. $100 Contact: W. C. Wiederholt, MD, 7010 Via Valverde, La Jolla 92037. (714) 459-8443.

November 6—**Bilateral Cleft Lip and Palate—Problems of Diagnosis and Treatment—8th Annual Symposium.** St John's Hospital and Health Center, Santa Monica. Saturday Contact: Cleft Palate Service, St. John's Hosp. and Health Ctr., 1328 22nd St., Santa Monica 90404. (213) 829-5511 ext. 2745.

November 6-7—**Dermatologic Surgery—Skin Grafting.** UCSF Saturday-Sunday.

November 11-12—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

November 13—**Flexible Bronchofibroscopy Workshop.** PMC Saturday. $250.

November 13—**Ophthalmological Emergencies for Emergency Department Physicians and Nurses.** Memorial Hospital Medical Center of Long Beach. Saturday. $50. Contact: Exec Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

December 2-3—**Medical and Surgical Complications of Uveitis** UCSF. Thursday-Friday.

December 3-4—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 1[illegible] hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hosp. Med. Ctr., 1225 15th St. Santa Monica 90404. (213) 451-1511, ext. 2148.

December 3-5—**Electronystagmography Workshop.** PMC a Golden Gateway Holiday Inn, San Francisco. Friday-Sunday

December 3-5—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Friday-Sunday. $300; $150 for residents.

December 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

December 9-11—**Trauma.** American College of Surgeons a Mark Hopkins Hotel, San Francisco. Thursday-Saturday $125. Contact: Frank R. Lewis, MD, Dept. of Surgery, San Francisco General Hospital, San Francisco 94110.

December 11—**Anesthesia Update: New Agents and Techniques** Valley Anesthesia Society of Sacramento, UCD and Calif Society of Anesthesiologists at Red Lion Inn, Sacramento Saturday. Contact: John H. Eisele, MD, Dept. of Anesthesiology, UCD School of Medicine, Davis 95616.

January 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday

January 14-15—**Surgical Symposium.** Santa Clara County Surgical Society and San Jose Surgical Society at LeBaron Hotel, San Jose. Friday-Saturday. 16 hrs. $125. Contact Lawrence Stern, MD, 2505 Samaritan Dr., Suite 606, San Jose 95128, (408) 358-1801; or Joseph Brozda, MD, 25 N 14th St., Suite 460, San Jose 95112, (408) 287-7434.

January 17-21—**Otologic Surgery Course—12th Annual.** Ear Research Institute, Los Angeles. Saturday-Wednesday. 4[illegible] hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 23-27—**Midwinter Clinical Convention.** Research Study Club of Los Angeles at Hilton Hotel, Los Angeles. Sunday Thursday. Contact: Research Study Club of Los Angeles Inc., Box 49412, Los Angeles 90049. (213) 879-0143.

January 26-28—**Advances in Neurology.** See Medicine, January 26-28.

January 28-30—**Pediatric Anesthesiology—15th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $125. Contact: Wayne Herbert, MD, Prog. Dir., CHLA, 4650 Sunset Blvd., Los Angeles 90054. (213) 660-2450, ext. 2262.

January 30-February 2—**Theodore Billroth Surgical Anatomy Course.** LLU. Sunday-Wednesday.

January 31-February 4—**Management of Trauma.** UCSD at Sheraton-Harbor Island, San Diego. Monday-Friday.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

October 21-22—**Old Age—Program on Geriatrics.** UCSF at Veteran's Home of California, Napa. Thursday-Friday.

October 23—**Fall Symposia—2nd Annual.** West Park Hospital at Sportsmen's Lodge Restaurant, Studio City. Saturday. 5 hrs. $25. Contact: Mrs. Barbara Bowden, Med. Staff Sect., West Park Hospital, 22141 Roscoe Blvd., Canoga Park 91304. (213) 340-0580, ext. 264.

October 24-27—**California Academy of Family Physicians.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: William R. Rogers, Exec. Sec., CAFP, 9 First St., San Francisco 94105. (415) 982-6091.

October 25-29—**Family Practice Review.** LLU. Monday-Friday.

October 25-29—**Global Medicine and Diseases of Travel—120th Annual Scientific Meeting.** Hawaii Medical Association at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., HMA, 510 S. Beretania St., Room 201, Honolulu 96813. (808) 536-7702.

October 29-30—**Behavioral Medicine: Strategies for Health Behavior Change.** USC. Friday-Saturday.

October 30-31—**Physiology of Respiration.** UCSF. Saturday-Sunday.

October 31-November 5—**American Association of Blood Banks—29th Annual Meeting.** Hilton Hotel, San Francisco. Sunday-Friday. Contact: Lois James, Asst. Exec. Dir., AABB, 1828 L St., NW, Suite 608, Washington, D.C. 20036. (202) 872-8333.

November 1-5—**Intensive Care.** STAN. Monday-Friday. $250.

November 1-5—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday.

November 5-6—**Clinical Electromyography.** See Surgery, November 5-6.

November 6—**Bilateral Cleft Lip and Palate—Problems of Diagnosis and Treatment.** See Surgery, November 6.

November 7-12—**American Academy of Physical Medicine and Rehabilitation.** Town and Country Hotel, San Diego. Sunday-Friday. Contact: C. C. Herold, Exec. Dir., AAPMR, 30 N. Michigan Ave., Suite 900, Chicago, Ill. 60602.

November 11-12—**Emergency Medicine (Advanced Course).** UCSF. Thursday-Friday.

November 11-12—**New Concepts in Medicine.** California Hospital Medical Center, Los Angeles. Thursday-Friday. 11 hrs. $25. Contact: K. L. Senter, MD, Dir., Med. Ed., Calif. Hosp. Med. Ctr., 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

November 12—**Diuretics.** USC. Friday.

November 12-14—**Primary Care—2nd Annual Postgraduate Seminar.** Stanford; Mission Bay Hospital, San Diego; Hyatt Medical Management Services, Encino, at Del Monte Hyatt House, Monterey. Friday-Sunday. Contact: Jay Beeler, Dir. of Public Relations, Hyatt Medical Management Services, 16633 Ventura Blvd., Suite 1325, Encino 91436. (213) 990-2000.

November 13—**Ophthalmological Emergencies for Emergency Department Physicians and Nurses.** See Surgery, November 13.

November 15-19—**Dermatology for Primary Care Physicians.** UCSF. Monday-Friday. $400. Intensive preceptorial course presenting practical management of skin diseases that constitute a large part of daily practice. Enrollment limited to 10 primary care providers.

November 29-December 3—**Advances in Diagnosis and Treatment in Clinical Medicine.** See Medicine, November 29-December 3.

December 1-3—**Immunizations—Review and Predictions.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

December 2-5—**Treatment of Sexual Dysfunctions.** USC at Canyon Hotel, Palm Springs. Thursday-Sunday.

December 9-11—**Genetics.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday.

December 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

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OCTOBER 27, WEDNESDAY—Preregistration

OCTOBER 28, THURSDAY—SCIENTIFIC SESSIONS

Selected Problems in Pulmonary Disease
*RALPH C. JUNG, MD, Associate Professor of Medicine, USC-School of Medicine

Pediatric Respiratory Emergencies
*GERALDINE Y. DYER, MD, Attending Physician, USC-School of Medicine

Current Problems in Pediatrics
*SHERRILL D. KOLODNY, MD, Private Practice, Fountain Valley

OCTOBER 29, FRIDAY

Recent Changes in the Worker's Compensation Law and How They Affect the Doctor
MR. JERROLD M. WOLF, Attorney at Law, Law Offices of Jackson, Balowitz, Wolf & Delaney, Santa Ana

Physicians' Rights in a Complex Society
MR. JOHN F. MOUNIER, JR., Attorney at Law, Law Offices of Rust & Armenis, Sacramento

The Practicality of Screening for Cancer
ROBERT C. COMBS, MD, Associate Dean-Continuing Medical Education, UCI-California College of Medicine

OCTOBER 30, SATURDAY

Profit Sharing Pension Plans, Sec. 79 and Corporation Deductible Insurance
MR. HAL SHULMAN and MR. BERNIE WEISSMAN, Philmar Associates Ins. Agency, Inc., Los Angeles

Advances in the Diagnosis of Pancreatic Disease
J. EDWARD BERK, MD, Professor of Medicine, UCI-California College of Medicine

Status Report on UCI-California College of Medicine
STANLEY van den NOORT, MD, Dean, UCI-California College of Medicine

OCTOBER 31, SUNDAY

Snakes, Spiders and Witches
FINDLAY E. RUSSELL, MD, PhD, Professor of Neurology and Biology, USC-School of Medicine

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101 City Drive South
Bldg. 53, Room 105
Orange, CA 92668; (714) 634-0152

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Credit: 10 hours CMA Category 1

January 10-14—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Sheraton-Harbor Island, San Diego. Monday-Friday.

January 13-14—**New and Old Antibiotics.** USC. Thursday-Friday.

January 18-21—**Diagnosis and Management of Seizure Disorders.** UCLA at Palm Springs. Tuesday-Friday.

January 22—**Gerontology.** John Muir Hospital and Walnut Creek Based Educational Committee at John Muir Hospital, Walnut Creek. Saturday. Contact: Marshall Y. Kremers, MD, 2528 Ptarmigan Dr., No. 3, Walnut Creek 94595. (415) 938-0568.

January 22-23—**Biofeedback and Meditation: Stress and Self-Regulatory Therapies.** UCSF and The Institute for the Study of Human Knowledge. Saturday-Sunday. 12 hrs. Contact: Ms. Mae Ling Yee, Cont. Ed. in Health Sciences, Room 135G, UCSF. (415) 666-2894.

January 22-February 27—**Basic Acupuncture.** PMC. Saturdays and Sundays. $1,100.

January 23-28—**Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sunday-Friday.

January 24-28—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

January 29—**Hypertension.** USC. Saturday.

January 31-February 5—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation —32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education. Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Family Practice Center, Health Sciences Center, Portland 97201:

Every Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School.

Providence Hospital, 700 N.E. 47th Avenue, Portland 97213:

October 6—Elevated Uric Acid: To Treat or Not to Treat—8:00 a.m.

October 13—New Developments in Viral Hepatitis—8:00 a.m.

November 3—Mechanisms of Drug Hepatotoxicity—8:00 a.m.

November 10—Pathogenesis of Acute Gouty Arthritis—8:00 a.m.

FUTURE DIRECTIONS IN CARDIAC PACING

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1977 Winter Conference Schedule

BETH ISRAEL HOSPITAL
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JANUARY 22 TO JANUARY 29, 1977
Vail Internal Medicine Conference
FEBRUARY 12 TO FEBRUARY 19, 1977
Vail Family/General Practice Conference
FEBRUARY 19 TO FEBRUARY 26, 1977
Vail OB/GYN Conference
FEBRUARY 26 TO MARCH 5, 1977
Aspen Radiology Conference
MARCH 5 TO MARCH 12, 1977
Vail Psychiatry Conference
MARCH 12 TO MARCH 19, 1977
Vail General Surgery Conference

For registration information: Call or Write
Beth Israel Hospital Conference Program
1818 Gaylord St., Denver, CO 80206
(303) 320-5333

November 24—Medical and Surgical Audit Review—8:00 a.m.
December 1—The Adult Respiratory Distress Syndrome—8:00 a.m.
December 8—Biofeedback in Medicine—8:00 a.m.
December 22—Staphylococcal Disease: Selected Aspects of Diagnosis and Treatment—8:00 a.m.

'AMILY PRACTICE

:very Thursday, 8:00 a.m. to 9:00 a.m.—**Family Practice Grand Rounds.** Family Practice Center, University of Oregon Medical School, Portland. Contact: David D. Smith, MD, Department of Family Practice, University of Oregon Medical School, Health Sciences Center, Portland 97201.

)ctober 21-22—**Family Practice Seminar** at Providence Hospital, Portland. Contact: Department of Family Practice, Providence Hospital, 700 N.E. 47th, Portland 97213.

)F INTEREST TO ALL PHYSICIANS

)ctober 1—**Oregon Gut Club Symposium.** University of Oregon Health Sciences Center, University Hospital South, 8B60, Portland. Contact: Clifford Melnyk, MD, Department of Gastroenterology, University of Oregon Health Sciences Center School of Medicine, Portland 97201.

)ctober 14—**Cancer of the Breast.** Portland Adventist Hospital, School of Nursing, Portland. Contact: T. R. Flaiz, MD, 6040 S.E. Belmont, Portland 97215.

ctober 21-22—**Annual Postgraduate Course in Surgery and Medicine.** Providence Hospital, Portland. Contact: Joseph E. Gambee, MD, Department of Family Practice, Providence Hospital, 700 N.E. 47th Avenue, Portland 97213.

ctober 29-30—**Third Annual Symposium on Critical Care Medicine.** Jantzen Beach Thunderbird, Portland. Contact: Oregon Society for Critical Care Medicine, Roger L. Klein, MD, Department of Anesthesiology, University of Oregon Health Sciences Center, Portland 97201.

VASHINGTON, ALASKA, IONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

October 15-17—**Western Dialysis and Transplant Society Annual Meeting.** Friday-Sunday. Olympic Hotel, Seattle. Physicians, $30; others, $20. Contact: Linda J. Huprich, Convention Mgr., 11633 Ventura Blvd., Encino, CA. (213) 981-0554.

October 22-23—**Aging and the Elderly.** Friday-Saturday. Seattle. Location to be determined. 9 hrs. Physicians, $60; others, $40. Contact: Pat Lind, Div of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

October 22-23—**Sports Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

October 25-29—**The Endocrine Society's Twenty-Eighth Annual Postgraduate Assembly.** Monday-Friday. Olympic Hotel, Seattle. 31½ hrs. $185. Contact: Mrs. Nettie C. Karpin, Exec. Secty., The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20014.

November 1—**Internal Medicine Review: Dermatology.** Monday. Univ. of Wash. in Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

November 2—**Internal Medicine Review: Dermatology.** Tuesday. Univ. of Wash. in Yakima. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

November 4-5—**Current Concepts in Drug Therapy.** Thursday-Friday. Seattle. Location to be determined. 12½ hrs. Physisians, $60; others, $30. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 11-12—**Arthritis.** Thursday-Friday. Seattle. Location to be determined. 12 hrs. $60. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 12—**Newer Approaches to the Same Old Headaches.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

November 12-13—**Human Genetics.** Friday-Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 17—**Allergy.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 293-3101.

November 18—**Internal Medicine Review: Medical Genetics.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

November 19—**Internal Medicine Review: Medical Genetics.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

November 19—**Treating the Untreatable.** Friday. Spokane. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 22—**Internal Medicine Review: Nuclear Medicine.** Monday. Univ. of Wash. in Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

November 23—**Internal Medicine Review: Nuclear Medicine.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

November 30—**Surgery: Shock and Clinical Fluid Balance.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Leonard W. Brewer, MD, 2833 Ft. Missoula Rd., Missoula, MT 59801. (406) 728-6815.

December 1—**Surgery: Shock and Clinical Fluid Balance.** Wednesday. Univ. of Wash. in Billings, Mont. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

December 10—**Psychiatry for the Non-Psychiatrist.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 7 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

December 16—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

December 17—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

December 27—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

December 28—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

January 7—**Medicine and the Law I.** Friday. Seattle. Location hours, fee to be determined. Contact: Pat Lind, Div. of CME HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195 (206) 543-1050 or 543-9495.

January 11-14—**Fluid and Electrolyte Balance.** Tuesday-Friday 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. 8 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98410. (206) 756-3152.

January 13-14—**Pediatrics.** Thursday-Friday. Seattle. Location hours, fee to be determined. Contact: Pat Lind, Div. of CME HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195 (206) 543-1050 or 543-9495.

January 19—**Perinatal Health Care.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave. Anacortes, WA 98221. (206) 293-3101.

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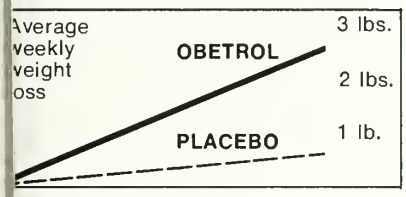

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ctions: Amphetamines are sympathomimetic amines with NS stimulant activity. Peripheral actions include elevation of stolic and diastolic blood pressures and weak bronchodilator d respiratory stimulant action. The anorectic effect diminishes er a few weeks.

dications: Exogenous obesity, as a short term (a few weeks) junct in a regimen of weight reduction based on caloric striction. For patients in whom obesity is refractory to other easures.

ontraindications: Advanced arteriosclerosis, symptomatic rdiovascular disease, moderate to severe hypertension, hyperyroidism, known hypersensitivity or idiosyncracy to the mpathomimetic amines. • Agitated states. • Patients with a story of drug abuse. • During or within 14 days following the ministration of monoamine oxidase inhibitors, hypertensive ses may result.

arnings: Tolerance to the anorectic effect usually develops thin a few weeks. When this occurs, the recommended dose ould not be exceeded in an attempt to increase the effect, ther, the drug should be discontinued. Amphetamines may pair the ability of the patient to engage in potentially hazdous activities such as operating machinery or driving a motor hicle; the patient should therefore be cautioned accordingly.

ecautions: Caution is to be exercised in prescribing amphetnes for patients with even mild hypertension. Insulin requirents in diabetes mellitus may be altered in association with e use of amphetamines and the concomitant dietary regimen. nphetamines may decrease the hypotensive effect of guanetidine. The least amount feasible should be prescribed or spensed at one time in order to minimize the possibility of erdosage.

verse Reactions: *Cardiovascular:* Palpitation, tachycardia, evation of blood pressure. Central nervous system: Overstimulion, restlessness, dizziness, insomnia, euphoria, dysphoria, mor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

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*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine

INDICATIONS For the relief of moderate to moderately severe pain

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children. PERCODAN®-Demi, containing half the amount of oxycodone, can be considered. (See product prescribing information for PERCODAN®-Demi.)

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may be occasionally necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN® is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE Signs and Symptoms Serious overdose with PERCODAN® is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume), Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN® may, in addition, result in acute salicylate intoxication.

Treatment Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

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Gastric emptying may be useful in removing unabsorbed drug.

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81% to 88% cure rate*

Gantanol® B.I.D.
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4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

Basic therapy with convenience and economy in acute nonobstructed cystitis†

†due to susceptible organisms

ROCHE

Please see following page for summary of product information.

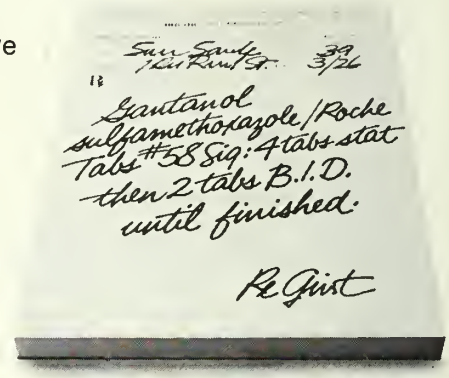
Gantanol® B.I.D.

sulfamethoxazole/Roche

Basic therapy with convenience and economy in acute nonobstructed cystitis*

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

- Effective in nonobstructed cystitis.
- Active against susceptible strains of gram-negative and gram-positive organisms: *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*
- Rapid antibacterial blood and urine levels—in from 2 to 3 hours.
- Convenient, economical B.I.D. dosage.
- Contraindicated during pregnancy and the nursing period and in infants under 2 months of age.
- As with all sulfonamides, adequate fluid intake should be maintained during therapy; perform frequent CBC's and urinalyses with careful microscopic examination.



*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily nonobstructed pyelonephritis, pyelitis and cystitis) due to susceptible organisms, usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.* **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and sclera injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

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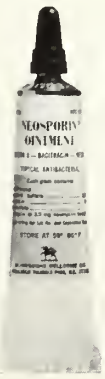
Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: Therapeutically (as an adjunct to systemic therapy when indicated) for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing. **CONTRAINDICATIONS:** Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components. **WARNING:** Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended. **PRECAUTIONS:** As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. **ADVERSE REACTIONS:** Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.



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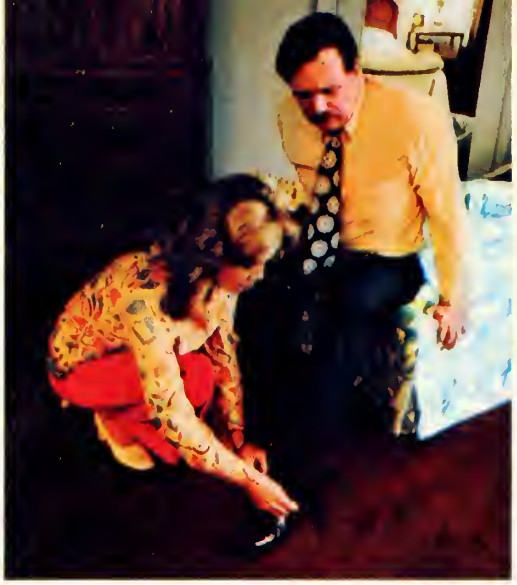

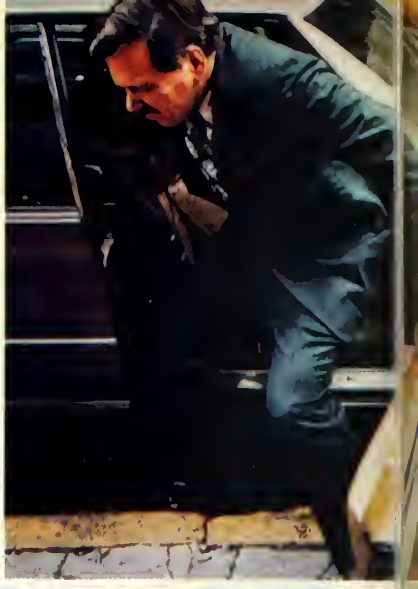

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In acute, painful low-back disorders

Soma® 350

(carisoprodol) 350 mg tablets

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Indications: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.
Contraindications: Acute intermittent porphyria and allergic or idiosyncratic reactions to carisoprodol or related compounds such as meprobamate, mebutamate, tybamate.
Warnings: *Idiosyncratic Reactions* Rarely, extreme weakness, transient quadriplegia, dizziness, ataxia, temporary vision loss, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation have appeared within minutes or hours of the first dose. These usually subside in several hours but supportive and symptomatic therapy, including hospitalization, may be necessary.
Pregnancy and Lactation: Safe use not established; weigh potential benefits against potential hazards in pregnancy, nursing mothers (concentrations in breast milk are two to four times that in plasma), or women of childbearing potential.
Children Under Twelve Not recommended.
Potentially Hazardous Tasks. Driving a motor vehicle or operating machinery.
Additive Effects: Effects of carisoprodol and alcohol, other CNS depressants or psychotropic drugs may be additive.
Drug Dependence Use cautiously in addiction-prone patients.
Precautions: To avoid excess accumulation, use caution in patients with compromised liver or kidney function.
Adverse Reactions: *Central Nervous System* Drowsiness, dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, idiosyncratic reaction (see "Warnings").
Allergic or Idiosyncratic: In previously unexposed patients, these are usually seen after 1-4 doses and include rash, erythema multiforme, pruritus, eosinophilia, fixed drug eruption with cross reaction to meprobamate. Asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension and anaphylactoid shock may be manifestations of severe reactions. In such cases, stop carisoprodol and initiate appropriate treatment (e.g., epinephrine, antihistamines, corticosteroids).
Cardiovascular. Tachycardia, postural hypotension, facial flushing.
Gastrointestinal. Nausea, vomiting, hiccup, epigastric distress.
Hematologic. Leukopenia and pancytopenia (on carisoprodol plus other drugs).
Usual Adult Dosage: One 350 mg tablet three times daily and at bedtime.
Overdosage: Has produced stupor, coma, shock, respiratory depression, and, very rarely, death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Empty stomach, treat symptomatically; cautiously give respiratory assistance, CNS stimulants, pressor agents as needed. Carisoprodol is metabolized in the liver and excreted by the kidney. Diuresis and dialysis have been used successfully with related drug meprobamate. Carefully monitor urinary output; avoid overhydration; observe for possible relapse due to incomplete gastric emptying and delayed absorption.
Before prescribing, consult package circular or latest PDR information.

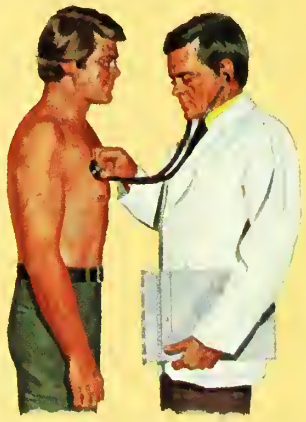
[1] Hindle, T.H. III: Calif. Med 117:7 (Aug.) 1972. 2,3. Unpublished Data on file, Medical Department, Wallace Laboratories, Cranbury, N.J.

Narrowing down pneumonias

Upjohn

Bacterial or nonbacterial?

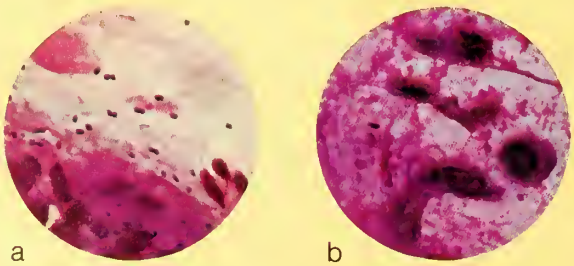
In the early stages of mild to moderate pneumonia, it is often difficult to reach an accurate bacteriologic diagnosis. A tentative differentiation may be made on history-taking, physical examination, CBC with differential analysis, and microscopic study of the sputum smear. Specimens should be obtained for culture and sensitivity testing, but when a bacterial pneumonia is diagnosed, therapy is often instituted before the etiological agent is positively identified.



Bacterial pneumonias may have a sudden onset with a shaking chill, rapid development of fever, pleuritic pain, and cough productive of rust-colored sputum. The Gram-stained sputum smear generally shows polymorphonuclear neutrophils as well as a predominance of the causative organisms. These are likely to be *Streptococcus pneumoniae,* still by far the most frequently encountered agent in bacterial pneumonia.[1] The CBC reveals marked leukocytosis with a shift to the left.

In *nonbacterial pneumonias*—mycoplasmal or viral—classical symptoms tend to develop more slowly, with myalgia, lassitude, and headache predominating. Sputum production is usually scanty, and the sputum smear is relatively uninformative, showing gram-positive cocci and other organisms which are part of the normal pharyngeal flora. The leukocyte count is normal or slightly elevated.

Direct Gram-stained sputum smears. (a) Pneumococcal pneumonia—note abundant polymorphonuclear leukocytes, as well as gram-positive diplococci. (b) Nonspecific—consistent with viral or mycoplasmal pneumonia. Note large mononuclear cell, as well as a few polymorphs and mixed bacterial flora (pharyngeal contaminants).



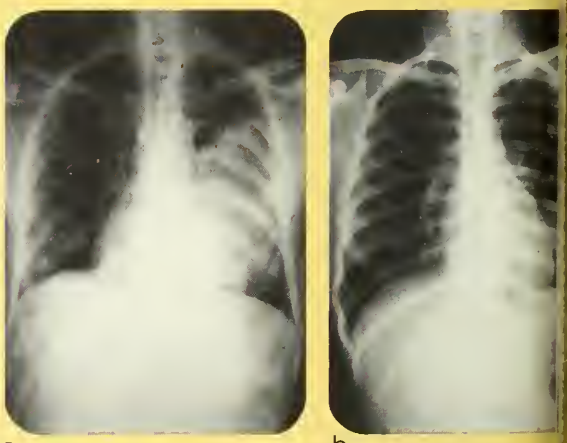
a b

Mycoplasmal or viral?

Differentiation between mycoplasmal and viral pneumonias may be impossible in the acute sta

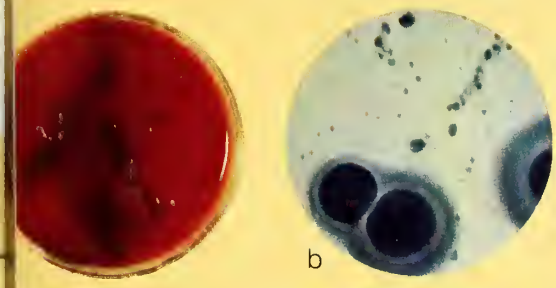
Serologic testing and culture methods for *Mycoplasma pneumoniae* are complex and time consuming, taking as long as two weeks after obtaining samples. The sensitivity and specifici the test for cold agglutinins have been question The complement-fixing antibody test may reflec previous infection. Furthermore, facilities for cul *M. pneumoniae* are not widely available.[3]

If treatment is to be initiated, therefore, it ma necessary to start on the basis of a *presumptive* diagnosis of mycoplasmal pneumonia.[1-3] In rea such a diagnosis, the physician relies on clinica judgment, considering such factors as the age c patient and the history of exposure. For example *Mycoplasma pneumoniae* is considered the mo common cause of pneumonia among ambulator patients aged 20 to 35.[1]



a b

Chest x-rays of patients with (a) pneumococcal pneumonia—classically heavy, extensive infiltration of left lung; (b) mycoplasmal pneumonia—mild infiltrate confined to left lower lobe. Roentgenography usually does not help in differential diagnosis, since both types of pneumonias may present with a wide spectrum of x-ray as well as clinical findin



istinct mucoid colonies of type 3 pneumococci *(Streptococcus moniae)* on sheep blood agar showing greenish discoloration a-hemolysis) of medium. (b) Typical "fried-egg" colonies of *plasma pneumoniae* consisting of dense central core with r periphery. Cultural and serologic methods for detecting *eumoniae* are complex, time-consuming, and not widely able.

Expectant therapy

atient with a presumptive diagnosis of lasmal pneumonia or bacterial pneumonia, it desirable to initiate antibiotic therapy before and sensitivity results are available.
ourse of erythromycin or tetracycline is ered effective in the treatment of mycoplasmal onia to help speed the clearing of infiltrate and the duration of symptoms.[1,3] In pneumococcal onia, erythromycin is an effective alternative to in, the drug of choice. A recent report, based from 200 hospitals of 100 beds or more, found *S. pneumoniae* sensitive *in vitro* to mycin.[4]
ong these therapeutic agents, only mycin provides effective coverage of both *asma pneumoniae* and *S. pneumoniae*. The ins are not effective against *Mycoplasma*, and *moniae* has shown a relatively high incidence ance to tetracycline.
n erythromycin is selected for therapy, (erythromycin enteric-coated tablets, Upjohn) d choice. E-Mycin is administered and ed as active erythromycin base, and may be i.d., q 6h, or b.i.d., immediately after meals or n meals. Thus, patients can use mealtimes to m remember their medication. The enteric on E-Mycin tablets helps ensure efficient ion in the intestinal tract, and bioavailability show that E-Mycin can be expected to e predictable, acceptable blood levels. The of E-Mycin helps assure economical therapy.
ycin rarely causes serious side effects and is ciated with liver toxicity.* The most frequent ects are upper gastrointestinal, such as nal cramping and discomfort, and are dose-Nausea, vomiting, and diarrhea occur ntly with usual oral doses. Serious allergic s, including anaphylaxis, have rarely been d.

ly in patients with severe liver impairment

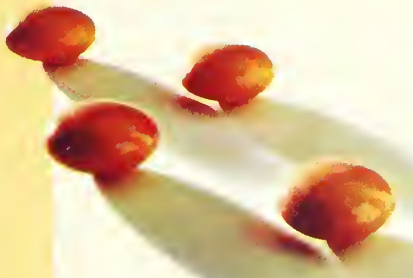
ES: 1. Chusid EL, Dalrymple W, Holloway WJ, et al Managing the infectious *Patient Care* 9:122-167, 1975. 2. The occasional might of mycoplasma *ed* 7:82, 85, 1975. 3. Stevens DA: Viral and Mycoplasma pneumonias. *d* 55:81-86, 1974. 4. Data source: PMR Bacteriologic Report, Winter Series 1975-1976. Data are a compilation of laboratory reports submitted during December 1975 and January and February 1976 by 200 acute care hospitals of 100 beds or more

Summary

Because pneumonias may be difficult to differentiate at the outset, treatment is often initiated before a causal diagnosis is made. However, readily available diagnostic criteria occasionally allow early differentiation between bacterial and nonbacterial pneumonias. When the diagnosis appears to be nonbacterial pneumonia, further differentiation between mycoplasmal pneumonia and viral pneumonia is more complex and time-consuming. Therefore, therapy is often initiated on the basis of a *presumptive* diagnosis of mycoplasmal pneumonia.

Erythromycin is an effective antibiotic against *Mycoplasma pneumoniae, Streptococcus pneumoniae,*† and *Streptococcus pyogenes.*† E-Mycin (erythromycin enteric-coated tablets, Upjohn) is administered and well absorbed as the active base, may be taken immediately after meals or between meals, and is essentially nontoxic.

†Although penicillin remains the drug of choice against these organisms, erythromycin is an effective alternative



E-Mycin® 250 mg

erythromycin enteric-coated tablets, Upjohn

wide-ranging usefulness in pneumonia*

*Mild to moderately severe, due to susceptible organisms

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001, U.S.A.
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Please turn page for brief summary of prescribing information.

Wide-ranging usefulness in pneumonia*

E-Mycin® 250 mg

erythromycin enteric-coated tablets, Upjohn

Upjohn

- For mild to moderately severe infections due to susceptible organisms that commonly invade the respiratory tract
- Essentially nontoxic (see Precautions and Adverse Reactions below)
- Documented bioavailability
- May be taken immediately after meals or between meals
- Active base formula produces predictable blood levels
- Formulated for quality...priced for economy

E-MYCIN® TABLETS — 250 mg — For Oral Administration (erythromycin enteric-coated tablets, Upjohn)
E-Mycin Tablets are specially coated to protect the contents from the inactivating effects of gastric acidity and to permit efficient absorption when administered either immediately after meals or when given between meals on an empty stomach.

Indications: *Streptococcus pyogenes (group A beta-hemolytic streptococci):* Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity. Parenteral benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. When oral medication is necessary (because the parenteral route is contraindicated) or if there is known allergy to penicillin, the following recommendations made by the American Heart Association apply: 1) Oral penicillin G or V (where no allergy exists)—This is the drug of choice. Give for a minimum of 10 days; 2) Erythromycin—Give for a minimum of 10 days. A few strains of streptococci resistant to erythromycin have been reported.
Alpha-hemolytic streptococci (viridans group): Short-term prophylaxis against bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin. (Erythromycin is not suitable prior to genitourinary surgery where the organisms likely to lead to bacteremia are gram-negative bacilli or the enterococcus group of streptococci.)
Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistance may develop during treatment.
Diplococcus pneumoniae: Upper respiratory tract infections (eg, otitis media, pharyngitis) and lower respiratory tract infections (eg, pneumonia) of mild to moderate degree.
Mycoplasma pneumoniae (Eaton agent, PPLO): In the treatment of primary atypical pneumonia, when due to this organism.
Treponema pallidum: Infections due to this organism.
Corynebacterium diphtheriae and *Corynebacterium minutissimum:* As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers. In the treatment of erythrasma.
Entamoeba histolytica: In the treatment of intestinal amebias only. Extraenteric amebiasis requires treatment with other agents.
Listeria monocytogenes: Infections due to this organism.

Contraindication: Contraindicated in patients with known hypersensitivity to erythromycin.

Warning: Safety for use in pregnancy has not been established.

Precautions: Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Surgical procedures should be performed when indicated.

Adverse reactions: The most frequent side effects of erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose-related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses. During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted. Mild allergic reactions such as urticaria and other skin rashes have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

Treatment of overdosage: The drug is virtually nontoxic, though some individuals may exhibit gastric intolerance to even therapeutic amounts. Allergic reactions associated with acute overdosage should be handled in the usual manner—that is, by the administration of adrenalin, corticosteroids, and antihistamines as indicated and the prompt elimination of unabsorbed drug in addition to all needed supportive measures.

How supplied: 250 mg enteric-coated tablets—in bottles of 100 and 500 tablets, and in unit-dose packages of 100 tablets. Caution: Federal law prohibits dispensing without prescription.

For additional product information, consult the package insert or see your Upjohn Representative.

NAS-4

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*Mild to moderately severe, due to susceptible organisms.

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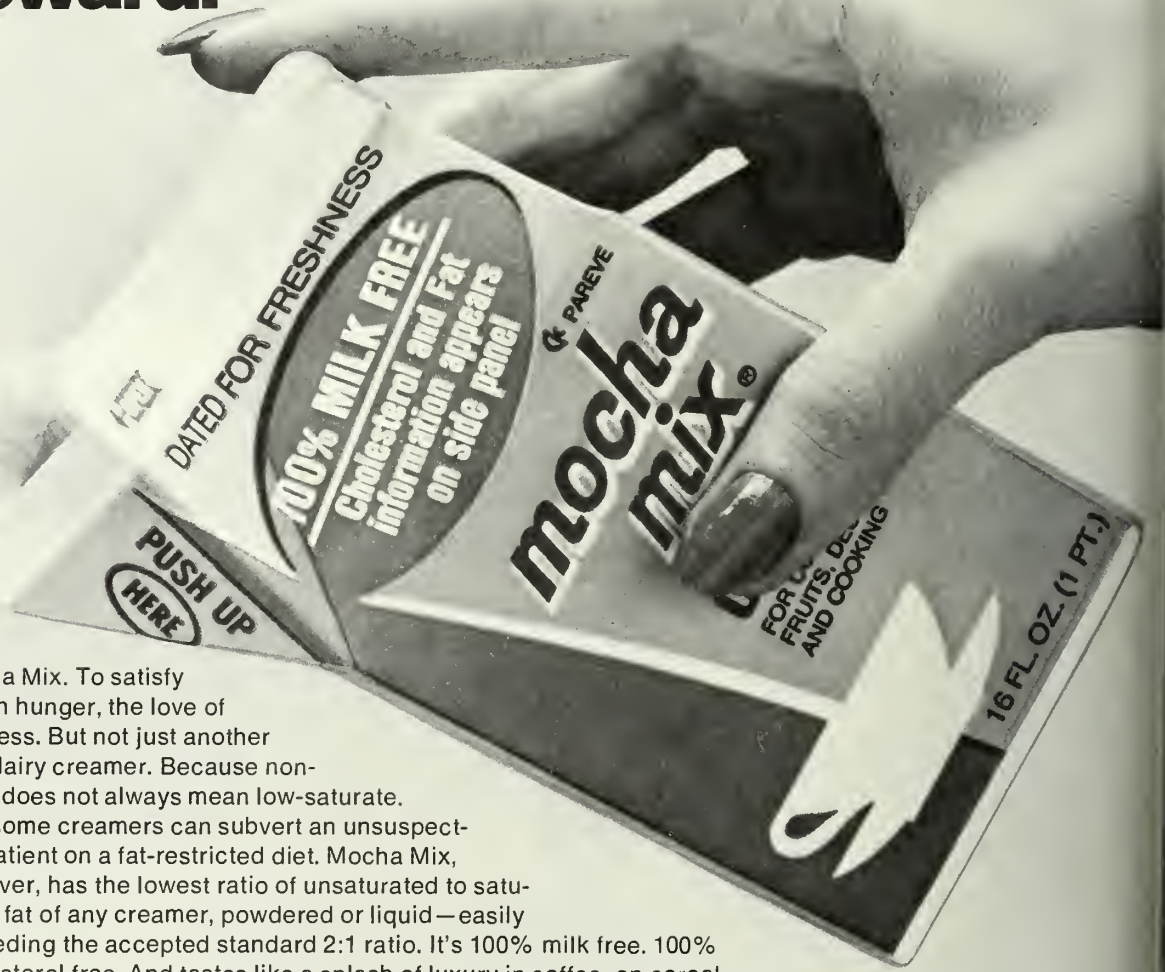
Offer a reward.



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MOCHA MIX DATA SHEET

Portion Size 1 Fluid Ounce (2 Tbs.)	
Servings per container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol	0

(Percentage of U.S. Recommended Daily Allowances (U.S., RDA)*

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

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breathes more activity into days and more rest into nights.
Please see summary of full prescribing information on the back of this page.

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Almost twice as effective as some other bronchodilators.

Brethine 5 mg was almost twice as effective as aminophylline 400 mg in a single-dose study. Brethine is twice as effective as ephedrine. And it has been shown to be more effective than metaproterenol.

If Brethine is added to theophylline, dosage should be titrated. Tablets of 2.5 mg and 5 mg are available.

Action may last up to 8 hours.

One tablet at bedtime, upon arising and at midafternoon may keep patients breathing comfortably through the night and day. Brethine contains no respiratory depressants (tranquilizers, sedatives or alcohol).

Minimal cardiac effect.

Brethine produces proportionally greater changes in pulmonary function than in heart rate or blood pressure.

Note: Patients should be advised that they may experien mild tremor when Brethine therapy is initiated.
With continued therapy, tremor usually diminishes while bronchodilation remains highly effective.

Brethine® brand of terbutaline sulfate Tablets 5 mg., Tablets 2.5 mg. *Before prescribing or administering, please consult complete product information, a summary of which follows:*

Tablets contain 5 mg (equivalent to 4 1 mg of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate

Indications: As a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema

Contraindications: Known hypersensitivity to sympathomimetic amines

Warnings: *Usage in Pregnancy:* The safety of the use of Brethine, brand of terbutaline sulfate, in human pregnancy has not been established. The use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother or child.

Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy

Adverse Reactions: Commonly observed side effe include nervousness and tremor Other reported reactio include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating These rea tions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency wit continued therapy In general, all the side effects observ are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 m in bottles of 100 and 1,000 and Unit Dose Packages of oval, scored, white tablets of 2.5 mg in bottles of 100.
(B) 98-146-060-E (Rev. 4/76)667004 C76-12

GEIGY Pharmaceuticals
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In serious gram-negative infections*

Three good reasons to initiate therapy with Garamycin® Injectable

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1. Unique spectrum.

2. Incidence of bacterial resistance is low and has not increased significantly.

3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

*Due to susceptible organisms

1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens. These are:

Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella, *Enterobacter*, *Serratia* } species

Garamycin Injectable is also highly effective against susceptible strains of **Staphylococcus aureus** and may be considered when penicillins are contraindicated.

2. Incidence of bacterial resistance is low and has not increased significantl

*In vitro** susceptibility virtually unchanged

* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study[1] in over 180 hospitals gram-negative pathogens identified and tested demonstrated high susceptibility t GARAMYCIN. From 1971 through 1975 there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator[2] where gentamicin ha been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance hav been reported.

References

1. P.M.R. Bacteriologic Reports—1971-1975.
2. Jackson, G.G.: Highlights of a Symposium on Gentamicin, a filmed panel discussion summarizing a symposium on gentamicin, University of California School of Medicine, Los Angeles, January 26, 1971.

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. Relatively low order of adverse enal and eighth nerve reactions hen used as directed.

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verse renal reactions

risk of adverse renal reactions is low in ents with normal renal function. Usually ifested by nitrogen retention as evidenced rising BUN and creatinine, they occur t often in patients with pre-existing renal age and in patients receiving er than recommended doses eated for longer periods of time than mmended. See Warning Box below.

Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.

A logical choice

in serious gram-negative infections†

pneumonia
urinary tract infections
septicemia
wound infections

† Due to susceptible organisms

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ARNING

Patients treated with GARAMYCIN Injectable should be der close clinical observation because of the potential icity associated with the use of this drug

Ototoxicity, both vestibular and auditory, can occur patients, primarily those with pre-existing renal damage, ated with GARAMYCIN Injectable, usually for longer riods or with higher doses than recommended

GARAMYCIN Injectable is potentially nephrotoxic, and s should be kept in mind when it is used in patients with e-existing renal impairment

Monitoring of renal and eighth nerve function is recom- nded during therapy of patients with known impairment renal function. This testing is also recommended in tients with normal renal function at onset of therapy who velop evidence of nitrogen retention (increasing BUN, PN, creatinine or oliguria). Evidence of ototoxicity re- ires dosage adjustments or discontinuance of the drug

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml should be avoided

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity

USAGE IN PREGNANCY Safety for use in pregnancy has not been established

See Clinical Considerations section which follows.

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WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

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USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura, fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema, nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION
GARAMYCIN Injectable may be given intram or intravenously.

For Intramuscular Administration:
Patients with normal renal function

Adults: The recommended dosage for GARAMYCIN Injectable for patients with seri infections and normal renal function is 3 mg./ administered in three equal doses every 8 hou

For patients weighing over 60 kg. (132 lb.), t dosage is 80 mg. (2 ml.) three times daily. For weighing 60 kg. (132 lb.) or less, the usual dos 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, d up to 5 mg./kg./day may be administered in th four equal doses. This dosage should be reduc 3 mg./kg./day as soon as clinically indicated.

In children and infants, the newborn, and p with impaired renal function, dosage must be in accordance with instructions set forth in the Package Insert.

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The intravenous administration of GARAM Injectable is recommended in those circumsta when the intramuscular route is not feasible (e patients in shock, with hematologic disorders, severe burns, or with reduced muscle mass).

For intravenous administration in adults, a s dose of GARAMYCIN Injectable may be dilut or 200 ml. of sterile normal saline or in a steri tion of dextrose 5% in water; in infants and chi the volume of diluent should be less. The conc tion of gentamicin in solution in both instance normally not exceed 1 mg./ml. (0.1%). The so infused over a period of one to two hours.

The recommended dose for intravenous ad tration is identical to that recommended for in muscular use.

GARAMYCIN Injectable should not be phy premixed with other drugs, but should be adm separately in accordance with the recommend of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectabl 40 mg. per ml., is supplied in 2 ml. (80 mg.) m dose vials and in 1.5 ml. (60 mg.) and 2 ml. (8 disposable syringes for parenteral administrati

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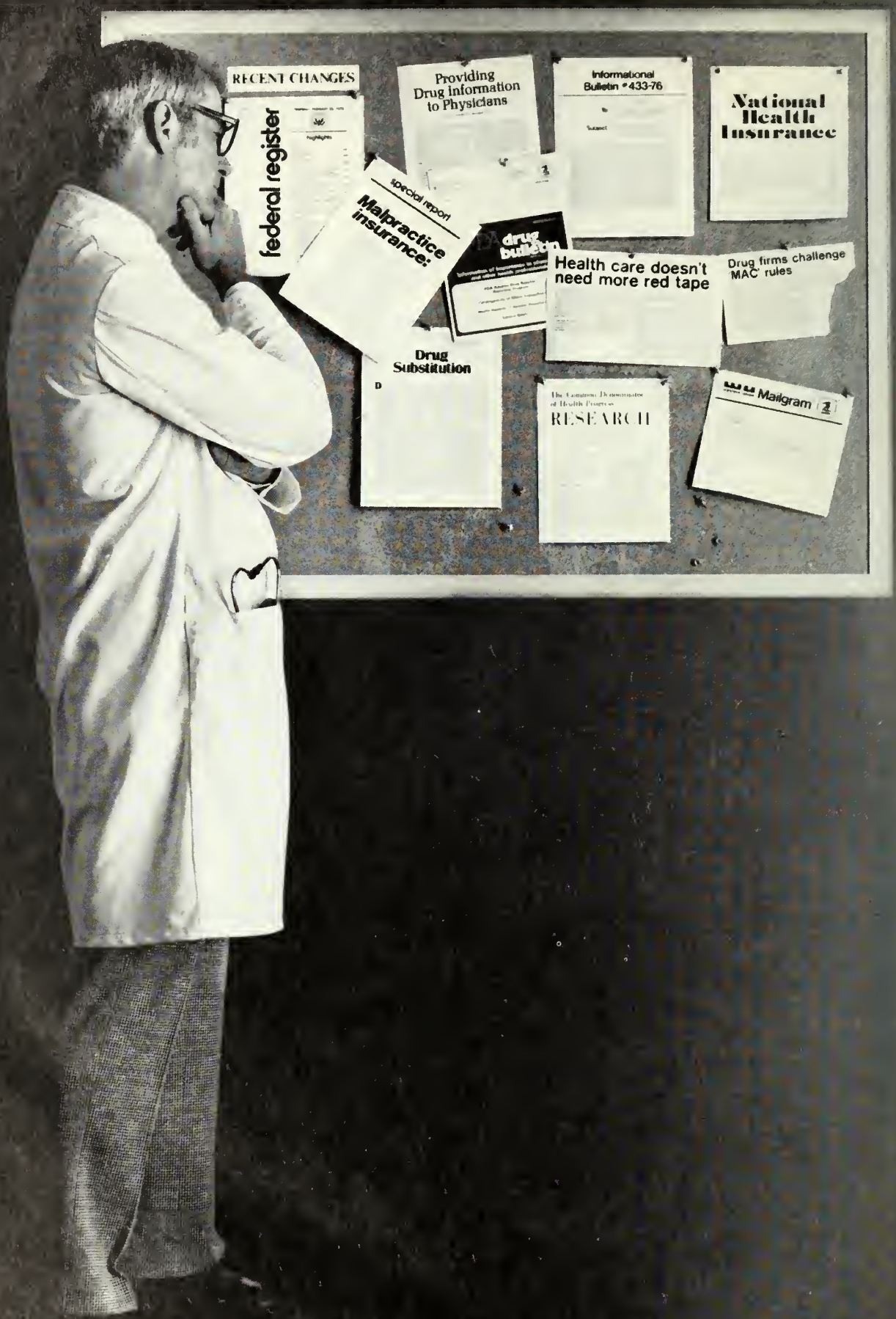
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Ironically, this dilution of physician control has ken place against a background of growing evidence at purportedly equivalent drug products may be inivalent, since neither present drug standards nor their forcement are optimal. In fact, the FDA itself says it s not enforced the same standards for hundreds of llow-on" products that it had applied to the original DA approvals. Thus physician control over patient rapy is being eroded with a risk that patients may be posed to drugs of uncertain quality.

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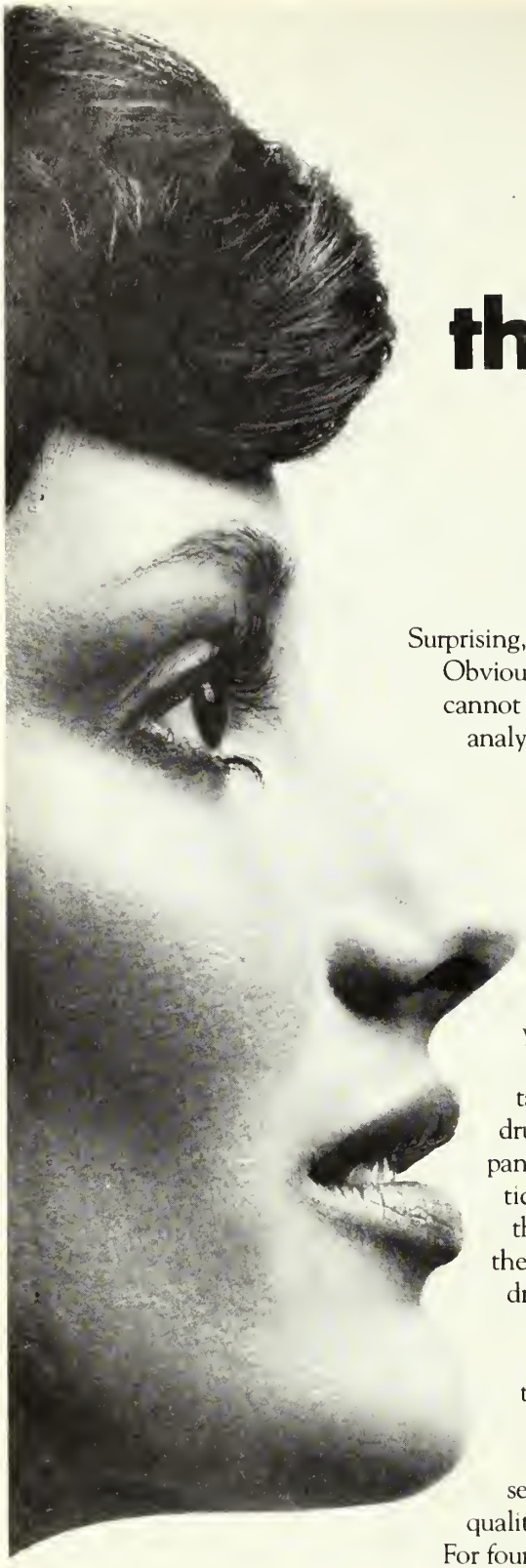

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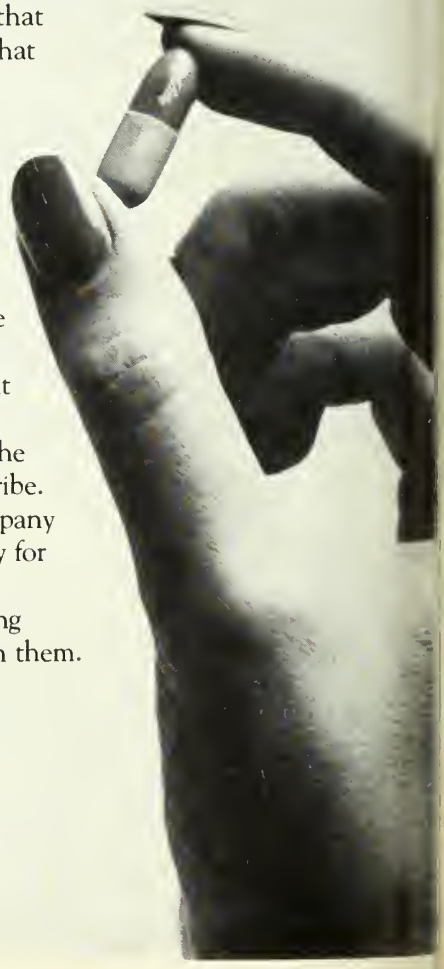

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THE WESTERN
Journal of Medicine

Potential Complications of Influenza A Infections

STEPHEN R. JONES, MD, *Portland*

DISEASE caused by influenza A virus is usually limited to uncomplicated respiratory infection. The infection assumes major medical importance because of the potential for a large number of persons to be infected within a short period (epidemic potential) and the severe consequences of the disease in some of those infected (excess mortality). Although nonrespiratory symptoms are often as predominant as respiratory ones, the extrapulmonary manifestations are not well appreciated and, though rare by comparison with the total number of people infected, may present with regularity since epidemics may affect 50 percent of the community. The purpose of this review is to analyze the complications of influenza: (1) those responsible for causing mortality, that is, respiratory complications, and (2) extrapulmonary complications.

Pulmonary Manifestations

The usual manifestations of influenza are well known, and respiratory symptoms are predominant. Upper airway inflammation may cause obstruction leading to bacterial infection (sinusitis or otitis). Laryngitis may cause croup in children and more rarely laryngeal obstruction in older children and adults.[1,2] This complication seems related to the epidemic strain.

It is probable that *uncomplicated influenza* is regularly associated with viral invasion of the lower respiratory tract as indicated in Table 1. The evidence for this is abnormalities noted on physical examination and studies of pulmonary function, even in patients in whom no abnormalities are seen on x-ray films of the chest. Rales are heard in a variable number of patients—the most important variable apparently is the examiner.[3,4] A variety of pulmonary functions have been shown to be abnormal in uncomplicated influenza. Restrictive abnormality, as defined by a forced vital capacity (FVC) of less than 85 percent of predicted or increasing 10 percent or more with convalescence, was documented by Johanson and co-workers.[5] That these changes were due to muscular weakness or pain is possible. In this series airway obstruction was found in only one patient. However, Leeder and associates[6] found increased airway resistance in 56 percent of patients by measuring the forced expiratory flow from 25 to 75 percent of the vital capacity (FEF_{25-75}), a sensitive index of small airway changes. Johanson and co-workers also provided evidence for impaired gas exchange at the alveolar-capillary level; in six of the ten patients there was an increased alveolar-arterial oxygen tension gradient which was associated with a low arterial oxygen pressure (Po_2). In both studies when patients were restudied at six week or six months, the values either had become normal or improved. These findings were confirmed by the studies of Horner and associates[7] who showed transient decrease in the diffusion capacity. However, in the patients in this study influenza had not been confirmed, only flu-like illness during an influenza epidemic. The transience of these abnormalities had led to the conclusion that influenza is not a significant factor in causing chronic lung disease.[8]

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Submitted March 3, 1976.
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ABBREVIATIONS USED IN TEXT

FEF_{25-75} = forced expiratory flow from 25 to 75 percent of the vital capacity
FVC = forced vital capacity

Pneumonia is the most feared complication of influenza. Various classifications of the pulmonary manifestation have been suggested in attempt to bring order out of clinical chaos. Louria and associates[9] divided the cases of patients admitted to the New York Hospital-Cornell Medical Center during the 1957-1958 epidemic into four groups:

- Physical findings without changes on x-ray studies.
- Secondary bacterial pneumonia.
- Acute pneumonia caused by virus alone.
- Concomitant viral and bacterial pneumonia.

Hers and associates[10] arrived at a similar grouping from their pathologic studies from the same epidemic. However, in the 1968-1969 epidemic (Hong Kong virus) the clinicians at the Mayo Clinic,[11] prepared to use these concepts, were unable to make clinical distinction easily between these groups. This was especially true in cases of localized pneumonia in which cultures for bacterial pathogens and virus were both positive. They concluded that simple classification on the basis of localized versus diffuse radiographic changes allowed prognostication. It is apparent that the prognosis of pneumonia with influenza depends on the amount of pulmonary parenchyma affected. Whether diffuse pneumonia is viral alone or viral with bacterial superinfection, the prognosis is grim. In localized pneumonia there is a much better prognosis, but apparently still there is greater associated mortality than in localized pneumonia in a period without influenza activity. It is probable that localized pneumonia is usually bacterial.

TABLE 1.—*Evidence for Lower Respiratory Involvement in Uncomplicated Influenza*

Finding	*Number Affected*	*Reference*
Rales	from 4 of 76	3
	to 13 of 16	4
↓FVC	6 of 10	5
↓FEF_{25-75} (MMFR)	9 of 16	6
↓DLco	20 of 20	7

DLco = diffusing capacity of the lung for carbon monoxide
FEF_{25-75} = forced expiratory flow from 25 to 75 percent of the vital capacity
FVC = forced vital capacity
MMFR = maximal midexpiratory flow rate

Until the 1957-1958 epidemic there was little evidence that influenza virus alone could cause fatal pneumonia. The clinicopathologic studies by Louria and co-workers thoroughly established that it can. In addition they showed that this was rarely a disease of normal persons, but a disease particularly seen in the presence of rheumatic mitral stenosis.[9] Although over-interpreted as a disease unique to mitral stenosis, this relationship has been observed by subsequent investigators.[11-13] It is also clear that other chronic diseases such as chronic renal failure, as well as other forms of heart disease, are at risk. The suggested common denominator is excess pulmonary fluid.[14] Clinical observations are supported by results of animal experiments showing that sublethal doses of virus can be made lethal by instillation of fluid into the lungs.[15] Presumably, the fluid allows diffuse spread of the virus. Since persons in whom such pathophysiology cannot be evoked do die of diffuse viral pneumonia, other factors must be important. The hypothesis that some persons are uniquely susceptible or resistant to influenza virus infection on a genetic basis has received a measure of recent support.[16] This study suggests that the lower antibody response to live influenza vaccine seen in persons with HL-A type W16 (histocompatibility antigen) is due to increased cellular resistance to infection.

Of the bacteria causing pneumonia after influenza, Staphylococcus aureus has received greatest notoriety. It has been isolated from most of the fatal cases.[17] However, it is equally well known that it is not the most frequent cause of pneumonia.[9,18] In their careful study of the 1968-1969 epidemic, and its effect on admissions for pneumonia at Grady Memorial Hospital, Schwarzmann and associates[18] showed the continued predominance of the pneumococcus and important occurrence of Gram-negative bacilli as the bacteria associated with pneumonia during the epidemic. Staphylococci became more common during the epidemic, but not predominant. The data in their study, as well as in most others[9,11-14] must be interpreted with caution since the finding of a bacterial cause was based upon expectorated sputum cultures and not more definitive means of specimen collection such as transtracheal aspiration or percutaneous lung aspiration. It is also of interest that the bacteria associated with influenza epidemics seem to vary from epidemic to epidemic and from geographic area to area within an epidemic.[18]

Extrapulmonary Manifestations

The analysis of extrapulmonary influenza is difficult. When half of the population is infected in an epidemic, then concurrent illness may be accompanied by clinical and laboratory evidence for influenza. Documentation can only be accepted with reasonable certainty when (1) the virus is isolated from the pathologically affected tissue under conditions making contamination unlikely or (2) there is a concurrent rise in the incidence of the associated condition pari passu the influenza —that is, an epidemiologic association.

Isolation of influenza virus from nonrespiratory tissue has been infrequent. During the 1957-1958 pandemic, Oseasohn and co-workers and Kaji and co-workers isolated the virus from extrapulmonary tissue.[19,20] The first report of viremia was by Naficy in 1963.[21] Subsequently others have also isolated influenza from blood.[22-24] In all but one of these reports,[24] the viremia occurred either during the incubation period or during the first 48 hours of illness. In addition to culturing the virus, Oseasohn and associates also showed histopathologic alterations in a variety of tissues.[20] In short, it is proven that viremia occurs with influenza, usually during the incubation period or quite early in the course of the disease, and pathologic alterations occur in extrapulmonary tissue from which the virus also has been isolated.

Cardiovascular

Although the heart seems to be the most acknowledged extrapulmonary tissue affected by influenza, the clinical and pathologic manifestations far exceed culture documentation. Both clinical myocarditis and pericarditis have been observed. It has been suggested that influenza-associated myocarditis can take two forms: (1) *immediate,* associated with fulminating disease[20] and (2) *delayed,* occurring during late convalescence.[25] Of the 33 fatal cases studied by Oseasohn,[20] in ten there were varying degrees of acute inflammatory disease of the myocardium. Eight patients were less than 40 years old. The mononuclear infiltrate varied from perivascular to diffuse. Virus was isolated from only one, although all were appropriately cultured. Other reports have not documented myocarditis at autopsy,[9] but it is obvious that the diligence of the search is an important variable.

Pericarditis, though clinically less a problem, is somewhat better documented.[26,27] In the report of Hildebrandt and co-workers,[27] the virus was isolated from pericardial fluid in a patient with pericarditis and effusion without pneumonia. The study of Woodward and associates[27] included only cases in which there were serologic changes and isolation of the virus from the respiratory tract. Neither myocarditis nor pericarditis has been shown to occur in epidemiologic concomitance with influenza.

Neurologic

The neurologic complications are the most diverse of any organ system.[28] Encephalitis caused directly by the influenza virus can be confused temporarily with the mental aberrations of the acute febrile illness encephalopathy. Acute encephalitis appears to have an epidemiologic connection with influenza. In the 1957-1958 epidemic, in particular, an excess number of cases of encephalitis appeared in England.[29,30] In addition the virus has been isolated from the brains of patients with encephalitis,[31,32] although the possibility of contamination at time of autopsy was not excluded. An encephalopathic syndrome has occurred after influenza, but like other "postviral" encephalitis, the pathophysiology remains unknown, though immunologic mechanisms are postulated. Concurrence of encephalitis lethargica and the 1918-1919 influenza epidemic has led to speculation that the two diseases shared common causes. This was 15 years before the viral cause of influenza was shown. This association has been of greater than usual interest because of the occurrence of parkinsonism months to years later in patients who had had encephalitis lethargica. The hypothesis that parkinsonism and influenza infection are related was strengthened, but not conclusively proved by the finding of influenza A antigen discretely in the hypothalamus and midbrain of six patients with postencephalitis parkinsonism but not in patients with idiopathic parkinsonism or other neurologic illnesses.[34]

The variability in the neurologic complications seen with various influenza epidemics has been noted and tropism of selected influenza strains demonstrated.[29]

Aseptic meningitis, myelitis[36] and Landry-Guillain-Barré syndrome[37] also have been associated on occasion with influenza. The hazards of overreading the association of influenza and neurologic disease during an epidemic are illustrated by Wells.[38]

Although diffuse, severe myalgia is a conspicu-

ous manifestation of influenza, at times surpassing in frequency the respiratory manifestations. Rhabdomyolysis with myoglobinuria was not described until the 1968-1969 epidemic, and then only in a single patient with well documented influenza who had had a history of several episodes of myalgia and dark urine preceded by self-limited febrile illnesses.[39] Indeed in a subsequent report, this 27-year-old man had another episode of myoglobinuria associated with a serologically documented Coxsackie B infection.[40] In 1973, during the A-2 (London) influenza epidemic, two patients had severe rhabdomyolysis and myoglobinuria and one had acute renal failure.[41,42] Both became aware of dark urine three to four days after the onset of the influenza. Findings on muscle biopsy studies showed rhabdomyolysis but no attempts were made to isolate the virus from muscle. A similar picture of objective myositis and elevated muscle enzymes has been reported in children with both influenza A and B.[43] Reye's syndrome (encephalopathy and fatty liver) has occurred after influenza A, as it has after numerous other viral infections.[44]

Hematologic

Disseminated intravascular coagulation has been associated with influenza virus infection, as it has with numerous other infective agents.[45,46] The severity of the process in the eight cases reported was appreciable and was associated with acute renal function impairment due to fibrin deposition. Thein and co-workers[47] reported that during an epidemic of influenza in Burma, in 196 (58 percent) of 380 children admitted to the Children's Hospital because of "hemorrhagic fever" (that is, usually with vomiting, hematemesis and a positive tourniquet test) there was serologic documentation of influenza A infection. These authors properly hesitate to make a direct association because the same clinical pattern was seen with other febrile illnesses, some of which were shown to be viral and some not. They suggested that a home remedy used widely by the Burmese may be responsible.

Renal

As mentioned, renal failure during the course of influenza has been reported.[46-48] In these nine reported cases, the onset of renal symptoms or signs (oliguria or hematuria) occurred only a few days after the onset of the influenzal symptoms. In four of the patients, findings on biopsy studies showed fibrin in the renal microvasculature and in these cases disseminated intravascular coagulation (DIC) was clinically established as well. In only one of the nine was DIC not mentioned as the most likely cause of renal failure.

In 1919 Goodpasture reported the case of an 18-year-old sailor who died of glomerulonephritis and pulmonary hemorrhage six weeks after a "typical" attack of influenza.[49] A similar case but with serologic documentation of the influenza was described by Wilson and Smith.[50] The diagnosis was supported by the finding of typical linear glomerular deposits of antiglomerular basement membrane antibody by immunofluorescence. Their hypothesis was that the influenza infection may have exposed the basement membrane antigens allowing circulating antibody to react with alveoli or may have induced antibody formation. The authors offer this as "a potential lead" in the understanding of the immunopathogenesis of this syndrome.

Host Defense Mechanisms

The association between influenza infection, whether covert or manifest, and subsequent bacterial infection (usually respiratory) has been mentioned. However, the relationship between other bacterial diseases is also of interest.[51] Both influenza and meningococcal disease most often occur in the winter, usually not together. In 1971 Eickhoff and associates reported that meningococcal colonization was more than five times more common in patients with evidence of recent Hong Kong influenza than in those without. Also in the 1968 epidemic Young and co-workers[53] recounted a simultaneous outbreak of group B meningococcal disease among 55 elderly women confined to a single ward in a mental institution. In all, the cases of 48 patients were studied. Influenza was present in 24 patients and meningococcal disease in 11 (attack rate 46 percent), while in the other half meningococcal disease was found in only 4 (attack rate 17 percent). On the other hand, patients with clinical meningococcal disease were no more likely to have had influenza than were those without meningococcal disease (62.5 versus 39.4 percent). There was no correlation between systemic meningococcal infection and concurrent influenza. However, there was a correlation between serological evidence of influenza and the meningococcal strain responsible for the epidemic. They concluded that influenza

did not predispose to meningococcal disease (blood stream invasion) or increase the likelihood of airborne dissemination of the meningococcus. They did feel that the data supported the hypothesis that the virus might alter certain host factors thereby enhancing meningococcal colonization after exposure—that is, the influenza infection created a locus minoris resistentiae.

Decreased skin-test reactivity to a battery of bacterial and fungal antigens has been shown to occur during influenza infection.[54] This was observed in only the cases of seven patients in whom there was serologically documented influenza, but not in four additional persons with symptomatically similar disease but in whom there was no laboratory evidence of influenza.

Altered mononuclear phagocyte function, specifically chemotactic responsiveness, has been shown both with *in vitro* infection of the monocytes as well as those taken from naturally infected patients.[55] The mechanism for this dysfunction is unknown, but direct inaction of the monocytes by the virus is likely. Alveolar histiocytes containing influenza antigen have been observed.[10] If the alveolar macrophages and the peripheral mononuclear phagocytes are similar in response to viral infection, then the increased susceptibility to airborne bacteria is easily understood since alveolar macrophages are an important component of the pulmonary defense mechanism. In addition, impaired granulocyte chemotaxis and phagocytosis has been reported with *in vitro* infection with influenza B virus.[56] This has been confirmed with influenza A virus but not with *in vivo* influenza infection.[57]

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Orally Given Hypoglycemic Drugs and Cardiovascular Disease

I feel that we should concede that there is perhaps a relationship between the use of orally given hypoglycemic drugs and cardiovascular disease . . . If we have conceded that there is a possibility of a problem inherent in the use of the oral agents, then I think we are on poor grounds to administer orally given hypoglycemic drugs to these patients . . . There is a problem in giving these patients insulin. One has to be very careful in its administration, simply because one does not want hypoglycemia to occur in patients who are being given insulin or who are receiving any form of therapy. The reason for this is that there is an outpouring of epinephrine in these patients as a response to their hypoglycemic state and even myocardial infarction has been seen on occasion, so one must be very careful in this group of patients.

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Enuresis: Causes, Cures and Cautions

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Enuresis is a common benign condition that affects up to 10 percent of school children. Innumerable causes have been proposed: emotional disturbances, small bladders, infections, allergies, polyuria and deep sleep. In an effort to modify abnormal sleep, drugs such as amphetamine or imipramine are frequently prescribed. Imipramine is often very effective but its acute toxicity is not fully appreciated by many patients or their parents. Since accidental imipramine overdose is a serious matter, strict rules regarding its storage and use must be enforced.

ENURESIS is a syndrome characterized by repeated involuntary micturitions after the age of about 5 years. If gross organic causes are evident it is more properly called incontinence. About 60 percent of patients have never experienced a symptom free period and are called *primary* enuretics. When relapse occurs after a long dry period (months or years) the condition is referred to as *acquired* or secondary. The overall course of the condition is benign as noted in the study of Oppel, Harper and Rider of 859 children.[1] In 90 percent of their patients initial dryness was achieved by age 7 and 97 percent were dry by age 12. They also showed that almost half of the bedwetters over age 6 were of the acquired type. The problem is more common among boys but the reported ratio varies widely from series to series.[2]

Causes

Investigations of this condition have generally concerned therapy and the basis upon which groups of test subjects are gathered is usually so unclear that evaluation of cause is difficult. Proposed causes of enuresis can be divided into two groups: somatic and psychogenic. The number of somatic abnormalities that have been proposed are many and can only briefly be touched upon here.

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There is evidence that in some primary enuretics there is reduced functional bladder capacity.[3] It is believed that these children maintain an infantile type of bladder control and, in the absence of voluntary mechanisms, are unable to enlarge their bladder capacity. When this enlargement is induced by consistently forced fluids and training in stopping and starting the stream, improvement often results.

Data have accumulated pointing to an association of sleep abnormalities with enuresis in some patients. Broughton has published an extensive review of the subject[4] and several surveys have shown an apparent connection between "deep sleep" and bed wetting.[5-7] Therapeutic trials using various alerter drugs have substantiated this connection[5,8,9] although drugs such as amphetamine or tricyclic antidepressants have many pharmacological effects unrelated to sleep.

Kjellberg found that over 20 percent of his series of enuretics showed definite evidence of low grade chronic trigonitis or urethritis[10] and others have reported comparable findings.[11] However, it is not generally believed by pediatricians that most primary enuretics have such minor organic problems.

Many parents of enuretics are convinced that in such children more urine than normal is produced. Except for children with sickle cell trait or disease, this has not been shown and Vulliamy's data show that enuresis is not associated with polyuria.[12]

That enuresis results from organic defects in the nervous system has been postulated. Several studies have disclosed a high incidence of electroencephalographic abnormalities in bed wetters as compared with controls[4,13] but such findings are not consistent.[2]

In the past, most pediatricians believed that enuresis was purely a failure of habit formation—inadequate training. While some studies have shown a significantly higher incidence among children of low socioeconomic classes, it would appear that the predisposition to bedwetting transcends family toilet-training techniques.[2] Many children with this problem have emotional disturbances but these are frequently the result rather than the cause of their symptom. There seems to be a good correlation between psychiatric factors and daytime wetting in aquired enuresis but most children with primary enuresis show no emotional causes and the results of psychotherapy are generally disappointing.

There is a remarkable degree of agreement between monozygotic compared with dizygotic twins with regard to enuresis histories.[14] This fact points strongly to a genetic basis for the disorder.

A number of physicians have proposed allergy as the cause of some cases of enuresis. They believe that various foods or chemicals can produce low grade bladder irritation with resultant urgency. No controlled studies have substantiated these findings.[15]

Cures

At present, treatment is often based upon the prejudices of the therapist. For those who accept the evidence that bed wetters maintain an infantile bladder control and are, consequently, unable to enlarge bladder capacity in a normal fashion, forcing of fluids during the day plus "bladder stretching" techniques are employed. In a cooperative child, results are often quite good after the child is able to hold 300 ml or more. There are no side effects.[3]

Physicians and parents inclined toward habit modification report excellent results using various pavlovian conditioning devices through which a few drops of urine close an electrical circuit and activate a bell or buzzer awakening the child automatically.[16] Again, this method is relatively safe although, if the alarm fails to awaken the child (a common situation), direct current from the apparatus travels through the adjacent skin and can produce indolent ulcers.[17]

Cholinergic blocking agents have been used for decades as primary or adjunctive therapy. Propantheline (ProBanthine®) is ineffective when given alone and the same is true for atropine and other belladonna mixtures.

The amphetamines have been employed with considerable success in some patients.[5,6,19] Reports of bedtime doses of d-amphetamine as high as 15 to 20 mg after which the child stays dry and yet sleeps are not uncommon. Such instances are emphasized by the "deep sleep" advocates as proof of their theory. As dosage increases insomnia eventually intervenes initiating a drop in dose. Mild nervousness is occasionally a problem but no serious toxicity usually occurs.[20]

Imipramine (Tofranil®) is effective in the treatment of some children with enuresis and its use has supplanted amphetamine. Many investigations over the past 15 years attest to this and several such studies were well controlled.[9,18] The drug is usually given a few hours before bedtime and the recommended dose is 25 to 50 mg in children from 6 to 12 years and as high as 75 mg in older patients. Most studies relating to efficacy do not clearly describe diagnostic criteria but it would seem that *primary* enuresis shows the greatest improvement with imipramine. After dryness is achieved, slow withdrawal of the drug is frequently followed by recurrences leading to repeated courses of therapy. This confronts the physician with a dilemma since the safety of long-term use of the drug in children has not been established.

Subacute toxicity of imipramine includes nervousness, insomnia, weight loss, syncope and vague gastroenteric complaints when using recommended doses. At these doses, cardiac toxicity is very rare in otherwise normal children[21] but this is not true for adults. Vague withdrawal symptoms have been reported.

Accidental or intentional acute overdosage is a very serious matter and represents a medical emergency.[22-24] Major symptoms occur after total acute doses of 10 mg per kg of body weight and include: convulsions, shock, coma, tachycardia, fever and cardiac arrhythmias including ventricular fibrillation (and death). Management of these situations is often difficult and imipramine is *not* dializable.[25,26]

Recently, Goel and Shanks reported their experience with 60 children poisoned with tricyclic antidepressants (imipramine or amitriptyline). Of these cases, 34 represented ingestion of drug

prescribed for enuresis, either for the patient himself or for a sibling.[22] These investigators commented that most of the parents regarded bed wetting as trivial and, consequently, the medicines prescribed for it as harmless. The authors raised the important question of whether the risks resulting from the broad availability of these compounds outweighed their benefits for bed wetters. Mofenson, Greensher and Horowitz[27] brought up the same question in 1972 as did Parkin and Fraser.[24] Fortunately, improved methods of treatment of imipramine overdose with intravenously given physostigmine are usually effective. Such treatment, as described by Rumack,[29] includes an initial therapeutic trial of 0.5 mg of physostigmine salicylate administered slowly intravenously. If signs of imipramine toxicity persist and no cholinergic effects are induced, the antidote can be readministered at five minute intervals up to a maximum total dose of 2 mg (up to 4 mg in adults). Physicians should not use intravenously administered physostigmine without being familiar with its undesirable effects and its contraindications.

Cautions

As long as imipramine is commercially available, it would seem that the following recommendations are reasonable concerning the treatment of enuresis.

- Prescribe imipramine only for children whose families understand that it is a dangerous drug and who will monitor its administration and storage with the same care as with digitalis or morphine.
- If the family is disorganized or unreliable, then imipramine should *not* be prescribed.
- When prescribed, imipramine should be dispensed in child-proof containers and should be locked up, and each prescription should be written for a small number of tablets.
- A 30-ml bottle of ipecac syrup (with instructions for use) should be in every home in which imipramine is stored.
- Strong consideration for nondrug regimens should be made for initial therapy of all bed wetters[28] in view of the benign natural history of the condition.[1]

It would also seem desirable that the manufacturer of imipramine modify its advertising literature and sales methods so that the above noted benefit to risk considerations are presented in a balanced fashion. Finally, it is urged that physicians in the United States report *all* treated cases of imipramine poisoning to the National Clearinghouse for Poison Control Centers (DHEW-FDA), regardless of the purpose of the original prescription, so that sound incidence and clinical toxicity data will be available to help monitor compliance with the above recommendations and to aid in formulating improved treatment recommendations.

Trade and Generic Names of Drugs

Dexedrine® ..... d-amphetamine sulfate
Tofranil® ..... imipramine hydrochloride
Elavil® ..... amitriptyline hydrochloride
Antilirium® ..... physostigmine salicylate

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Breast Reconstruction for Malignant or Premalignant Disease

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In ten patients breast reconstruction was done after surgical treatment for a premalignant or malignant breast disease. In six of these, prophylactic subcutaneous mastectomy and implant reconstruction were carried out, and in the remaining four reconstruction was done after simple or modified radical mastectomy. It is suggested that these procedures should be considered by those physicians and surgeons who undertake evaluation and treatment of breast disease in women. Breast reconstruction should be considered and offered to patients who suffer from the severe personal and emotional trauma attendant to surgical operation for breast disease.

THE SURGICAL TREATMENT for carcinoma of the breast has undergone pronounced changes in the last 20 years. McWhirter[1] first challenged the concept of radical mastectomy as being the treatment of choice, and the failure of such procedures as the Urban[2] extended radical mastectomy to produce superior results accelerated the trend toward less radical surgical operation. The procedures currently being advocated are partial mastectomy,[3] modified radical mastectomy or limited resection plus radiotherapy.[1,4,5] The treatment of *in situ* lobular carcinoma in particular has been cited as requiring much less than radical surgical operation. In fact, this entity has been challenged by Wheeler[6] as not being related to invasive carcinoma, and Haagensen[7] and others have abandoned mastectomy for lobular carcinoma *in situ* in favor of excisional biopsy.

Without debating the various surgical alternatives, two facts are emerging related to the recent trend toward limited excision. First, greater attention is now being focused on the need for reconstructive surgical procedures on the female breast after mastectomy. Second, women are rightfully demanding a greater role in deciding the choice of surgical procedures. This paper reports ten cases of breast reconstruction in the last three years. Six cases of subcutaneous mastectomy with reconstruction and four cases of reconstruction after mastectomy are presented and the surgical indications for each procedure are discussed.

Case Presentation

In six patients between the ages of 33 and 50 subcutaneous mastectomy with implant reconstruction was carried out (see Table 1). Four of these operations were for fibrocystic disease and

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two were for early ductal or lobular carcinoma confined to local tissue. Implant reconstruction was done immediately in three cases and delayed 10 to 24 months in three cases. In four of the six patients there were satisfactory cosmetic results (Figures 1 and 2) and in two patients there were contracted capsules, giving a somewhat firm, round and globular appearance to the breast.

In four patients breast contour restoration was done after simple or modified radical mastectomy. Diagnoses were adeno-, colloid, ductal and lobular carcinoma. Reconstruction with either gel or inflatable implants was delayed for 8 to 20 months. Results were cosmetically satisfactory in three of the four patients (Figures 3 through 5), with a contracted capsule in the fourth patient. There has been no recurrence of breast cancer in the three years of follow-up. Of interest is the fact that in one patient (number 8), reconstruction was successful after radiation therapy of 5,000 rads to the chest wall.

Discussion

Many series of subcutaneous mastectomies with breast reconstruction have been published.[8-11] Clinical situations in which subcutaneous mastectomy with implant reconstruction should be considered are listed below[12] (Table 2). (Note that we are not calling these conditions "indications" for subcutaneous mastectomies. The conditions are relative, and not absolute, because not all answers to the question of when to carry out this procedure have been determined, and not enough data have been collected over a long enough time to clearly define the "indications.") The clinical conditions are as follows:

- Multiple recurrent breast nodules in a premenopausal woman necessitating multiple surgical biopsies.
- Highly positive family history in a patient with nodular breasts.
- Extreme anxiety, concern or "cancerophobia" in a patient with persistent breast nodularity.
- Suspicious findings on a mammogram in patients with bilateral nodularity.
- Patients in whom there has been diagnosis on biopsy of fibrocystic disease, which has been frequently reported to carry an increased incidence of cancer versus the expected ratio in the female population at large.[13] (Of the varying histological types, intraductal hyperplasia with papillomatosis or sclerosis, and microcystic disease appear to be more frequently associated with cancer than does macrocystic disease.[14])

TABLE 1.—*Case Review in Ten Cases of Breast Reconstruction*

Patient	*Age*	*Diagnosis*	*Primary Surgery*	*Reconstructive Surgery*	*Results*
1 ...	50	Right lobular carcinoma *in situ*, Left ductal carcinoma	Bilateral subcutaneous mastectomy	13 months Subpectoral gel implants	Good cosmetic, No recurrence
2 ...	48	Mammary dysplasia fibrocystic	Bilateral subcutaneous mastectomy	24 months Suprapectoral gel implants	Good cosmetic
3 ...	46	Intraductal papilloma carcinoma	Bilateral subcutaneous mastectomy	Immediate Suprapectoral inflatable implants	Contracted capsule
4 ...	44	Fibrocystic disease	Bilateral subcutaneous mastectomy	Immediate Suprapectoral inflatable implants	Contracted capsule
5 ...	33	Fibrocystic disease	Bilateral subcutaneous mastectomy	Immediate Suprapectoral gel implants	Good cosmetic, Silicone granuloma
6 ...	43	Extreme cellular atypia	Right subcutaneous mastectomy	10 months Subpectoral inflatable implants	Good cosmetic
7 ...	36	Left lobular carcinoma, Right dysplasia	Left modified radical mastectomy, Right subcutaneous mastectomy	Left—19 months Suprapectoral gel implant, Right—6 months Subpectoral gel implant	Good cosmetic, No recurrence
8 ...	41	Infiltrating colloid carcinoma on right	Right modified radical mastectomy after 5,000 rads radiotherapy	20 months Gel implant	Good cosmetic, No recurrence
9 ...	37	Ductal adenocarcinoma	Modified radical mastectomy, Axillary node dissection	9 months Subpectoral gel implant	Good cosmetic, No recurrence
10 ...	53	Right lobular carcinoma, Left dysplasia	Right simple mastectomy, Left simple mastectomy	Right—8 months Suprapectoral inflatable implant, Left—immediate Suprapectoral inflatable implant	Contracted capsule

• Due to the relatively high incidence of bilaterality of breast cancer (sometimes quoted as up to 25 percent) in the contralateral breast, prophylactic subcutaneous mastectomy and implant replacement may be considered in such patients.

• Lobular carcinoma *in situ,* in particular, has been cited as having a great incidence of bilaterality. Wheeler,[6] Haagensen[7] and others have abandoned mastectomy in favor of limited biopsy and close follow-up for this condition. Subcutaneous mastectomy with reconstruction would remove the tissue at risk and lessen the patient concern as well as the necessity for frequent reevaluations.

It should be pointed out that studies have shown that 100 percent of breast tissue is never removed by subcutaneous mastectomy.[11] Residual breast tissue is most prevalent under the areola, in the axillary tail of Spence, and other peripheral locations. Indeed, some 24 cases of breast cancer occurring up to five years after subcutaneous mastectomy have now been recorded.[12] Although this frequency represents only a 0.5 percent incidence in cases reported in a large study, more cases will certainly arise as the group is studied through the years. On the other hand, in a large series of prophylactic subcutaneous mastectomies, a 2 to 6 percent incidence of the discovery of otherwise unsuspected breast cancer was reported.[12] Although this group presumably carried a high risk, since fibrocystic disease was present in all patients, perhaps many of these early occult cases would have gone undetected if not for the elective procedure.

Breast reconstruction after radical or modified

Figure 1.—Patient 1.—Appearance 13 months after prophylactic subcutaneous mastectomy for carcinoma *in situ.*

Figure 3.—Patient 7.—Appearance after modified radical mastectomy of the left breast and subcutaneous mastectomy of the right breast.

Figure 2.—Satisfactory cosmetic contour restoration after subpectoral gel implantation.

Figure 4.—Satisfactory contour restoration of both breasts with gel implants.

radical mastectomy is now being reported with greater frequency.[16-18] This procedure probably will be more common in the future as techniques and implants improve. For example, in one of our patients implant reconstruction was successful after radical mastectomy and radiation therapy. Therefore, radiation therapy, although making subsequent reconstruction more difficult, does not preclude it entirely. Radical mastectomy with skin graft, however, renders further reconstruction extremely difficult. Nipple reconstruction, combined with reduction of the opposite breast to achieve better symmetry, is often combined with contour restoration after radical mastectomy.

TABLE 2.—*Clinical Conditions in Which Subcutaneous Mastectomy with Breast Reconstruction Should be Considered*

- Multiple breast biopsies
- Positive family history
- "Cancerophobia"
- Suspicious mammograms
- Severe fibrocystic disease
- Protect contralateral breast from cancer
- Lobular carcinoma *in situ*

Figure 5.—Completed reconstruction with nipple restoration by labial graft.

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Branched Renal Calculi

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Surgical operation on 30 kidneys was carried out for branched renal calculi, with no operative mortality. Of 23 kidneys in which conservative surgical procedures were used, 83 percent are now stone-free. When all stones were successfully removed, cultures of urine were sterile in 80 percent of cases, but when fragments remained, no patient was infection-free. It was found that impaired renal function need not be a contraindication to surgical operation, and indeed that in five of seven patients with impaired renal function, serum creatinine levels either remained stable or improved. We believe that surgical removal is the most conservative management of branched renal calculi.

ALTHOUGH RENAL-CONSERVING surgical operation for branched renal calculi has been done for at least a hundred years, the very nature of these stones makes such operation potentially hazardous. Before ten years ago, because of the generally poor results and high complication rate, such surgical procedures never achieved widespread popularity despite scattered reports showing that operative intervention, including nephrectomy, was superior to medical management alone.[1,2] Blandy examined his experience with the unoperated staghorn calculus and concluded that expectant treatment led to nephrectomy, often for the dreaded complication of pyonephrosis, in half of the patients not operated on, and death from progressive renal failure in most of the remainder.[3,4] Technical advances in just the past decade[5-7] have made nonablative surgical operation for staghorn calculi common, if not routine, and the results fully support the contention that surgical intervention rather than expectant medical management is the more conservative treatment plan.[8,9]

We have examined our surgical experience with staghorn calculus to evaluate: (1) our success rate using a variety of surgical approaches, (2) the interrelationship of residual stone fragments, infection and stone recurrence and (3) the influence of impaired renal function on surgical suitability.

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Clinical Data

Since July 1970 we have evaluated the cases of 33 consecutive patients with 38 staghorn calculi, all but five of whom received surgical treatment. Of the five unoperated patients, two declined surgical treatment and three were considered medically unfit because of advanced age or severe heart disease with angina, in the presence of stable renal function. Of the remaining 28 surgical patients, there were 19 women and 9 men. Their ages ranged from 11 through 75 years. The presenting complaint was pain in 15 patients; in all but two urinary tract infection was present. In all, metabolic studies and preoperative and postoperative evaluation of renal function were made. Two patients had been previously treated for hyperparathyroidism, and one was known to have cystinuria.

Thirty surgical procedures were carried out in 28 patients (bilateral operations were done in two) (Table 1). Nephrolithotomy was done in ten patients using the technique described in 1967 by Smith and Boyce.[5] The term "anatrophic nephrotomy" was used by Smith and Boyce to suggest the all-inclusive concept of preoperative surgical measures and postoperative actions designed to minimize atrophy of the renal paren-

chyma. Selective renal hypothermia was used in all nephrolithotomies,[7] and intraoperative radiographic control was considered indispensable. In four patients, a nephrostomy tube was placed intraoperatively to permit Renacidin® irrigation. In nine patients, extended pyelolithotomy was carried out using the technique of Gil-Vernet,[6] with isolated nephrotomy in five and partial nephrectomy in two. In two other patients, stones were removed with partial lower pole nephrectomy alone. Seven primary nephrectomies were done, five because of nonfunction as shown by excretory urography and renal scan. Two followed attempted nephrolithotomies that were deemed unsuccessful intraoperatively because of the extent of parenchymal disease. In two patients, *ex vivo* or "bench" surgical procedures were done—that is, the procedures were carried out after nephrectomy while the kidney was sustained by extracorporeal pulsatile perfusion with cryoprecipitated plasma using the Travenol Viacell® perfusion apparatus (Travenol Laboratories, Morton Grove, Illinois). Both procedures were extended pyelolithotomies, one with multiple nephrotomies, and the other with a partial nephrectomy. Following successful removal of all stones, these kidneys were autotransplanted to the contralateral iliac fossa. Bench surgical operation was selected in the first case because of the dual presence of a staghorn calculus and a surgically correctable arterial lesion, and in the second because of the absence of most of the ureter as a result of surgical procedures done previously.

TABLE 1.—*Operative Procedures*

Anatrophic nephrolithotomy with local hypothermia	10
Extended pyelolithotomy with or without nephrotomy	7
Extended pyelolithotomy with partial nephrectomy	2
Partial nephrectomy alone	2
Bench surgery with extracorporeal perfusion (both extended pyelolithotomies)	2
Primary nephrectomy	7
	30

TABLE 2.—*Current Status (Average Follow-up, 25 Months)*

Stone free	19	(83%)
Conservative operations (23 kidneys)		
Immediately stone free	16	
Fragment passed (recurrence 1)	4	
Stone present	4	(17%)
Residual fragments	3	
Unchanged	2	
Enlarged	1	
Recurrence	1	

In all patients in whom conservative surgical procedures were done, specific antibiotic therapy was continued for at least six months postoperatively.

Results

Surgical

Patient follow-up now ranges from 3 to 63 months, for an average of 25 months. In all, 23 conservative procedures have been done in 21 patients, with 16 of the kidneys being rendered stone-free at the time of operation. In seven kidneys there were small retained stone fragments. In four of these, however, all fragments have subsequently passed spontaneously (Table 2). In two of the remaining three kidneys, residual fragments have shown no change in size, while one was enlarged slightly.

Four kidneys with retained fragments were treated by postoperative Renacidin irrigation.[10] One patient received an insignificant amount because of the onset of pain and a rash. Three kidneys were irrigated for a total of three, four, and six weeks respectively. Several fragments became slightly smaller, but only one disappeared completely, and that in a kidney with several fragments remaining. In this latter patient, all fragments subsequently passed and the patient also is free of infection.

In none of the patients in our series has a new stone formed in the contralateral unoperated kidney, and in only one patient has there been recurrence of a stone. Therefore, excluding the patients in whom nephrectomy was done, 19 of 23 kidneys in our series are free of stones at present—a cure rate of 83 percent.

Renal Function

In 20 of our 28 patients, preoperative levels of serum creatinine were normal and remained stable following operation. In eight patients, there was depressed preoperative renal function with either serum creatinine over 1.5 mg per 100 ml or creatinine clearance less than 60 ml per minute. Of these eight, conservative procedures were carried out in seven. In none of the patients was surgical operation not done because of impaired renal function. Postoperatively in five of these patients renal function either improved or showed no change, while in only two patients did renal function decline (Table 3). In one of these two patients, delayed nephrectomy was done for

TABLE 3.—*Impaired Preoperative Renal Function*

Patient	Pre-operative Cr/C_{cr}	Post-operative Cr/C_{cr}	Procedure
1 . . .	1.8/58	1.1/75	Anatrophic nephrolithotomy with contralateral nephrectomy
2 . . .	2.2/37	1.3/. .	Right pyelolithotomy; Left extended pyelolithotomy
3 . . .	1.9/30	1.6/. .	Extended pyelolithotomy
4 . . .	1.9/46	1.9/50	Extended pyelolithotomy
5 . . .	4.5/10	2.7/16	Extended pyelolithotomy
6 . . .	1.2/58	1.9/32	Bench; secondary nephrectomy
7 . . .	3.8/11	7.9/08	Anatrophic nephrolithotomy

Cr/C_{cr} = serum creatinine level/creatinine clearance

hemorrhage, although in this patient postoperative function before nephrectomy was improved over preoperative values. In the second patient there was a serum creatinine value of 3.8 mg per 100 ml and clearance of 11 ml per minute before surgical operation. Renal function at first was stable following nephrolithotomy (clearance 15 ml per minute one week after operation); however there was a slow but complete deterioration in renal function during the next 22 months.

One patient presented with a solitary kidney and a serum creatinine value of 10.3 mg per 100 ml with clearance of 2.5 ml per minutes. With correction of dehydration, we were able to improve the serum creatinine level and clearance to 4.5 mg per 100 ml and 10 ml per minute, respectively. Postoperatively, following successful removal of all stone fragments, these values improved further, to 2.7 mg per 100 ml and 16 ml per minute.

Infection

The close relationship between infection and the presence of stones has been supported by our data. Preoperatively, in 93 percent of patients infections were present despite previous appropriate antibiotic therapy. In 15, the infecting organism was Proteus, either alone or with Escherichia coli. E. coli alone accounted for another six. Postoperatively, in 12 patients infections are still present. To make a proper correlation between infection and presence of stones, however, we must

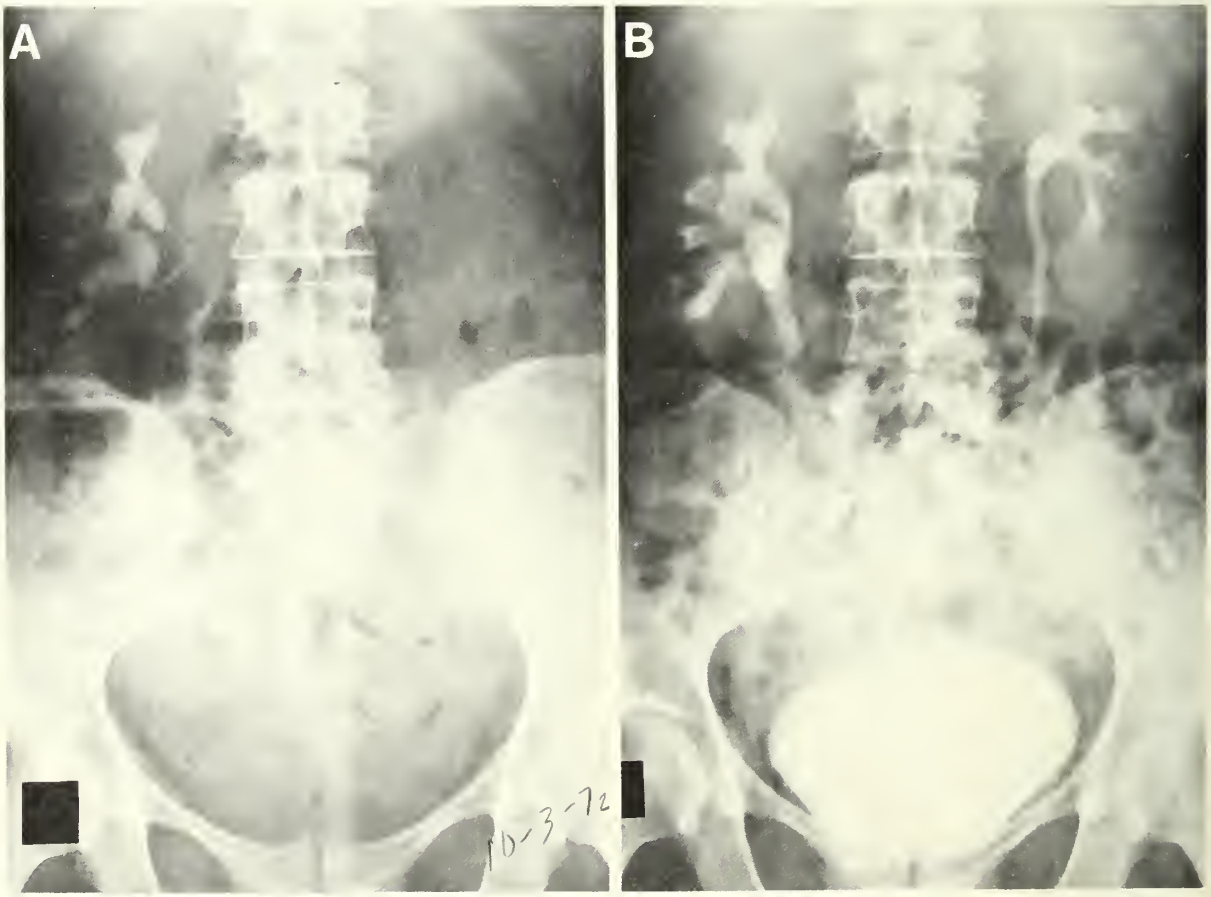

Figure 1.—(Case 1) **A**, Preoperative plain abdominal film showing moderate-sized branched renal calculus in right kidney, **B** Preoperative excretory urogram showing moderate obstruction from stone.

exclude four patients. In two patients in whom there are infections but no stones, indwelling Foley catheters have been placed for the neurogenic bladders, and in a third patient infected stones are present in the contralateral, as yet unoperated kidney. In a fourth patient, in whom a delayed nephrectomy was done for nonfunction, there are no stones but severe chronic pyelonephritis and an ileal loop diversion are present. Excluding these four, our overall postoperative infection rate is 33 percent. More important, however, when retained stones are present the infection rate is 100 percent; but when all stones have been removed the infection rate falls to only 20 percent.

Eighteen stones were crushed and cultured. Three stones were sterile and for the remaining 15 there were positive findings on cultures. Of 20 stones sent for crystallographic analysis, in 18 there were various proportions of magnesium ammonium phosphate (struvite) and apatite, the former usually predominant, and occasionally small amounts of calcium oxalate intermixed. Two stones (one patient with bilateral staghorns) were pure cystine.

Complications

There were three major complications in our series. A delayed nephrectomy was necessary for hemorrhage in a patient nine days after renal bench surgical operation with autotransplantation. In a second patient, nephrectomy was carried out for nonfunction and chronic infection 22 months after the original nephrolithotomy (Patient 6, Table 3). In a third patient there was a nonfatal pulmonary embolus after discharge from hospital. In all 30 operations, the average number of blood transfusions during and immediately following operation was two units. Average postoperative time in hospital was 15.3 days, but excluding those patients kept in hospital for prolonged periods for Renacidin irrigation reduces this figure to just under 11 days.

Reports of Cases

Several case histories will serve as representative examples.

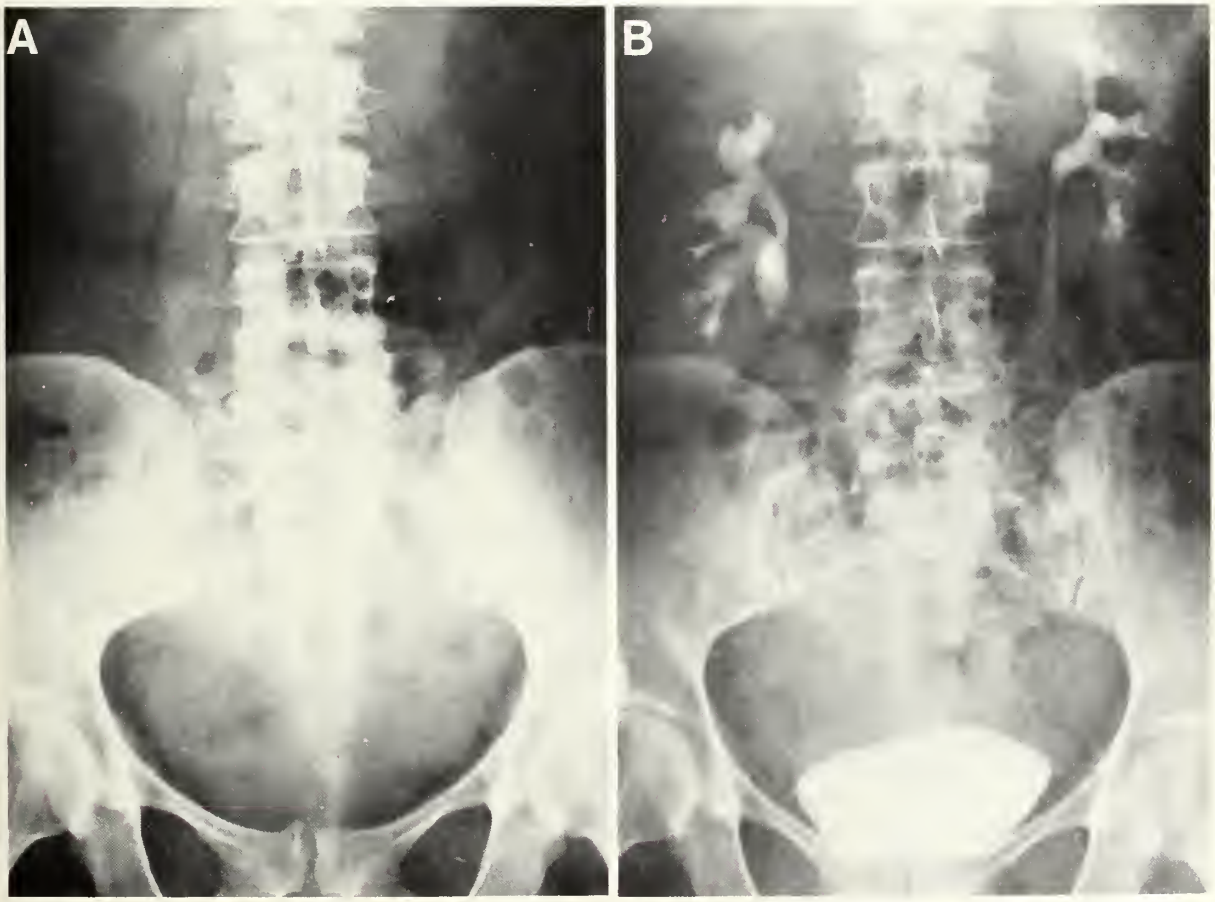

Figure 2.—(Case 1) **A**, Postoperative plain film showing complete removal of staghorn calculus. **B**, Excretory urogram three months after nephrolithotomy showing mild residual dilatation of right collecting system.

CASE 1.—In a 37-year-old white woman the first urinary tract infection occurred at age 30. Findings on an excretory urogram after a second infection two years later showed a large staghorn calculus with partial obstruction but good function (Figure 1). Because of flank pain, persistent Proteus mirabilis infection, and steady growth in size of stone, she was referred to the University of California, Davis—Sacramento Medical Center (UCD-SMC) for therapy in late 1972.

Findings on physical examination were unremarkable. The serum creatinine value was 0.8 mg per 100 ml with a clearance of 78 ml per minute. Calcium and phosphorus values were normal. Urine culture grew more than 100,000 colonies per ml of Proteus mirabilis. An arteriogram showed a single renal artery and good parenchyma.

On October 6, 1972 a retrograde pyelogram was carried out followed by an anatrophic nephrolithotomy under selective hypothermia. Ischemia time was 75 minutes, and there were no residual calculi shown to be present intraoperatively by kidney-sized x-ray cassettes.

Results of stone analysis showed struvite 60 percent and apatite 40 percent, and culture of the crushed stone grew Proteus mirabilis. Postoperative urine cultures were sterile until six months later, when again they grew more than 100,000 colonies per ml of Proteus mirabilis. On x-ray film, a 6×22 mm spindle-shaped stone was seen in the distal ureter; subsequently it passed spontaneously. Culture of this crushed stone also grew Proteus mirabilis. A follow-up excretory urogram ten months after the original surgical operation showed no stone fragments and good function (Figure 2), and urine culture was sterile.

CASE 2.—A 43-year-old black woman had onset of malaise, dysuria and frequency, and right flank pain in early 1970. After two years of treatment with antibiotics without appreciable relief, a period during which the patient lost 20 pounds, she was referred to UCD-SMC for definitive treatment.

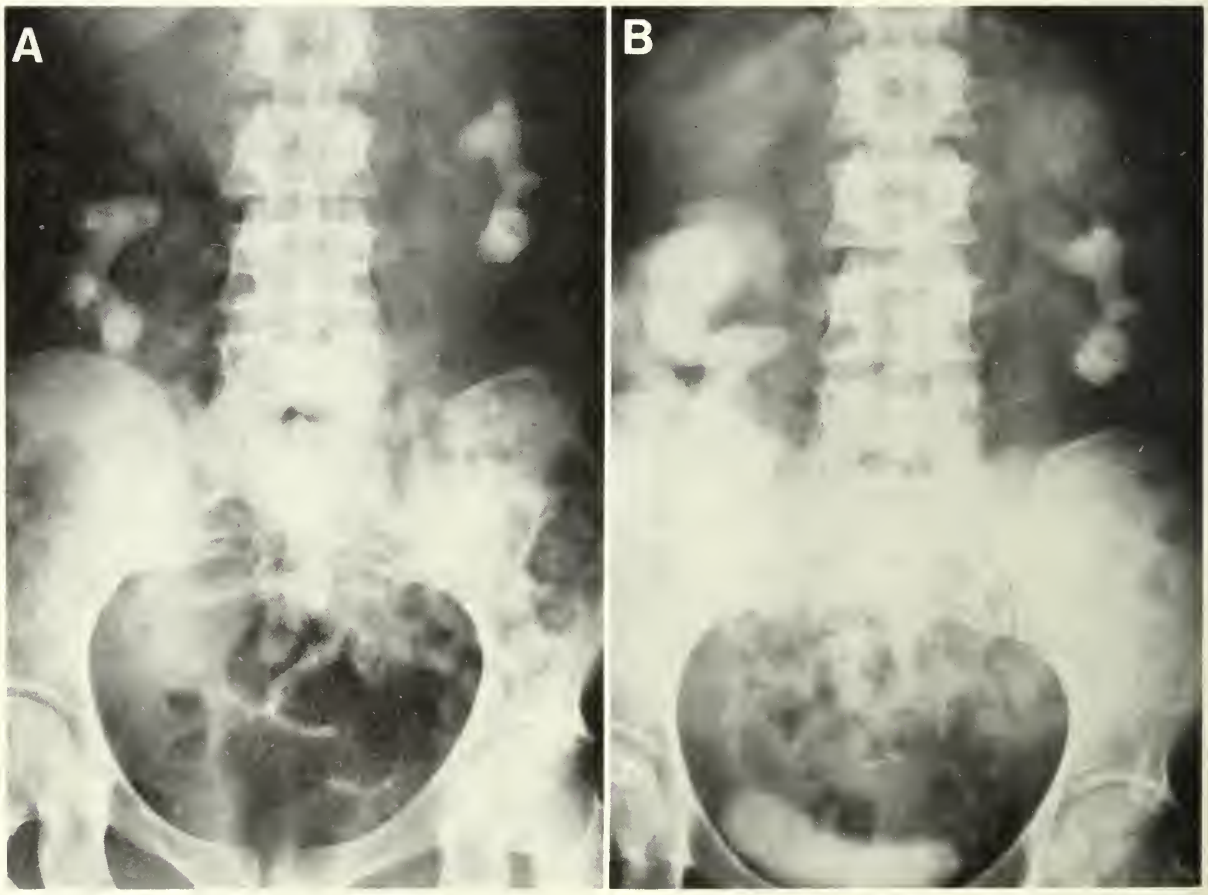

Figure 3.—(Case 2) **A**, Preoperative plain abdominal film showing bilateral staghorn calculi. **B**, Preoperative excretory urogram at one hour showing severe obstruction on right and nonfunction on left.

On physical examination at the time of admission the patient was seen to be thin and appeared chronically ill. A tender, ballottable mass in the right upper quadrant was noted. Hemoglobin level was 8.3 grams per 100 ml, calcium and phosphorus values were normal and the serum creatinine level and creatinine clearance were 2.1 mg per 100 ml and 60 ml per minute, respectively. Urine culture grew more than 100,000 colonies per ml of E. coli.

Findings on an excretory urogram included bilateral staghorn calculi, notably delayed function and hydronephrosis of the right kidney (Figure 3), and nonfunction of the left (confirmed by renal scan). An arteriogram showed pronounced cortical atrophy of the entire left kidney and the right lower pole.

On September 13, 1972 retrograde pyelography followed by an anatrophic right nephrolithotomy was carried out under selective hypothermia. Stone analysis showed 70 percent struvite, 28 percent apatite and 2 percent brushite; culture grew E. coli and Proteus mirabilis. On pathologic examination of the lower pole there was severe acute and chronic pyelonephritis with xanthogranulomatous reaction. One month later, exploration of the left kidney failed to show any potentially salvageable kidney, and a left nephrectomy was carried out. Postoperatively, the creatinine level fell to 1.5 mg per 100 ml and creatinine clearance improved to 75 ml per minute. Urine culture was sterile and on excretory urogram three months postoperatively no stone fragments were noted and there was improvement shown in right-sided hydronephrosis (Figure 4).

Discussion

At present the most popular surgical approaches for branched renal calculi are anatrophic nephrolithotomy, extended pyelolithotomy and partial nephrectomy. Each approach has its own proponents, but it has been our experience that no single operative procedure is adaptable to all clinical situations. Thoroughness of stone

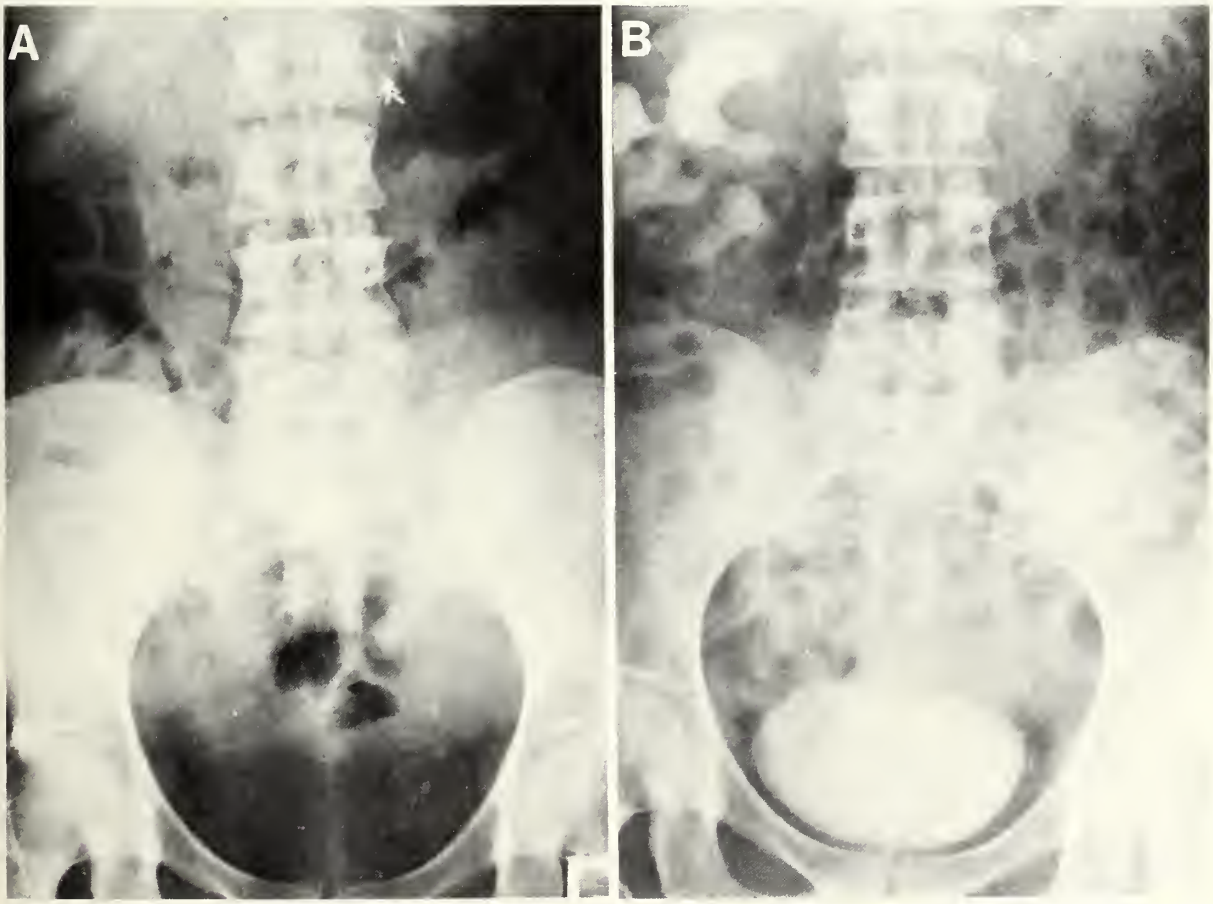

Figure 4.—(Case 2) **A**, Postoperative plain film showing no stones present. **B**, Excretory urogram two months after left nephrectomy and right nephrolithotomy with lower pole nephrectomy showing improvement in both obstruction and function.

removal (and thereby eradication of infection) and degree of preservation of functioning renal tissue assume major consideration in the selection of surgical approach.[5,6,10,11]

In our series of 23 conservative procedures, seven kidneys had fragments left at the time of operation, most of them very small. Four of these fragments remained following our first seven conservative procedures, and only three following our next 16. In four patients, it was not possible to locate fragments documented by intraoperative radiographs, but in three patients radiographs failed to show fragments subsequently found on postoperative films. Among the patients with retained fragments, in four the stones spontaneously passed postoperatively. Since this is not a rare occurrence in the literature,[8,11] it would seem important, if all stones cannot be completely removed, to assure that those retained be as small and as few as possible. Therefore it follows that any adjunct that might decrease the number or size of retained fragments, such as Renacidin irrigation, should be helpful. Others[15] have also supported the use of Renacidin irrigation in this manner, but it is important to remember that Renacidin irrigation of the upper tract is potentially hazardous and its use needs to be closely monitored.

Our series includes seven patients with impaired renal function preoperatively in whom conservative operations for stone removal were carried out. Although in two of these patients the kidney ultimately was lost, five of the original seven either improved or showed no change, and now have only mild functional impairment. Furthermore, although these patients did require slightly longer stays in hospital and higher blood replacement, all patients are alive today and in none of them has long-term hemodialysis been necessary. We believe that infected branched renal calculi may contribute substantially to azotemia and therefore should be removed unless such a procedure is contraindicated by other medical factors.

For many years the rate of recurrence following surgical removal of staghorn calculi was extremely high, this high rate being more the rule than the exception.[2] More recently, however, with improvement in surgical techniques and control of infection, recurrence rates have decreased considerably and vary from 5 to 33 percent in various series.[6,8,9,11] In our series, with careful bacteriologic follow-up, in only one patient has a renal calculus re-formed.

Because of the existence of bacteria deep within the stone, the inability of antimicrobials to penetrate to depths sufficient to kill those bacteria necessitates complete removal of the stone to eradicate infection.[10] Our series showed a postoperative infection rate of 100 percent when residual stone fragments were present, but only 20 percent when all stones were removed. The likelihood of stones re-forming in patients with residual infection is quite high because of the generally higher urinary pH in the presence of urea-splitting microorganisms and the decreased solubility of both struvite and calcium salts in an alkaline medium. Both Lavengood and Marshall[12] and Sutherland[13] have reported a lower stone recurrence rate in postoperative patients in whom urine cultures are sterile, compared with those patients in whom infection remains.

While renal bench surgical operation was highly successful in one of our patients with a branched renal calculus and renal artery disease,[14] in another it resulted in emergency nephrectomy for delayed hemorrhage. The indications for this highly-specialized type of surgical therapy must be critically applied and the risks must be clearly understood. Nevertheless, during evaluation and preoperative planning, this too must be given consideration in selecting the best possible surgical approach for patients with complex stone and associated renal disease.

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Screening for Syphilis in an Aged Psychiatrically Impaired Population

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A serum Venereal Disease Research Laboratories (VDRL) test was carried out in 216 elderly patients with dementia or "functional" psychiatric illness, or both, as part of a community based screening program. The VDRL test was positive in 13 patients, 11 of whom (5.1 percent) had an actual past or present syphilitic infection as confirmed by the fluorescent treponemal antibody absorption test (FTA-Abs). In six patients (2.8 percent) syphilis was newly detected, and in another two patients previously detected syphilis had been inadequately treated. Only two (0.9 percent) biologic false positive reactors were detected. These results question the belief that aging per se is a common cause of the biologic false positive reaction; and indicate a relatively high incidence of past or present syphilitic infection in geriatric patients with psychiatric illness in the community who have been referred for crisis intervention.

A NUMBER OF REPORTS have described the value of specialized diagnostic and placement services for older patients referred for psychiatric disorders.[1,2] Many of these patients suffer from unrecognized medical problems which manifest themselves in behavioral symptomatology. While the value of such services is no longer at issue, such programs are typically beset with economic difficulties and tend to limit the scope of their examination to the most relevant screening procedures.

One such procedure which has been reported to be of only marginal value in the aged is the Venereal Disease Research Laboratories (VDRL) serologic test for syphilis.[3] It is claimed that in 10 percent of all persons over age 70 years there are unexplained biologic false positive (BFP) reactions, and therefore that aging per se is a major cause of the BFP reaction.[4] Of 58 randomly selected elderly patients (average age 82 years) in institutions, in six there were persistently positive reagin tests for syphilis.[5] In none of these patients was specific antitreponemal antibody shown present, nor could any of the usual causes of the BFP reaction (such as autoimmune disease or cirrhosis) be found. Similar results were obtained in a study of serum specimens of 231 patients (mean age 70 years) in institutions, in whom 11 percent were BFP reactors.[6] A high incidence of BFP reactors was detected in men admitted to a Veteran's Administration hospital, two thirds of whom were over the age of 50. These studies suggest that although positive serologic tests for syphilis are a common phenomenon in the elderly population, the detection of an actual syphilitic infection is rare.

Procedures and Subjects

As part of its effort to deliver comprehensive crisis intervention services to elderly patients

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Submitted December 8, 1975.

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ABBREVIATIONS USED IN TEXT

BFP = biologic false positive
CSF = cerebrospinal fluid
FTA-Abs = fluorescent treponemal antibody absorption test
VDRL = Venereal Disease Research Laboratories

(over age 60) living in the community, the King County Outreach for Older Adults program in collaboration with the University of Washington Department of Psychiatry and Behavioral Sciences, carries out a routine screening evaluation for treatable causes of dementia or so-called "functional" psychiatric illness, or both, in its patients with identified neuropsychiatric problems. Included in this evaluation is the VDRL test for syphilis.

During the 18 months from March 1974 through June 1975, serum specimens of 214 consecutive patients were so examined. These persons were predominantly of northern European extraction, and represented all classes of the social spectrum. Mean age was 76.6 years, and the ratio of women to men was approximately 2:1. In all, 83 percent were living in the community, either alone or with family or friends. Only 17 percent were in institutions, usually in nursing homes because of dementia. The major diagnostic categories for those seen included dementia (67); dementia complicated by functional psychiatric syndromes (36); functional psychiatric syndromes in the absence of dementia (predominantly paranoid and affective syndromes) (59), serious medical or surgical illness (30) and alcoholism (22).

A quantitative VDRL slide flocculation test was carried out by the King County Department of Public Health. If positive, a fluorescent treponemal antibody absorption test (FTA-Abs), a sensitive and specific test for Treponema pallidum antibody, was done.

Results

In 13 patients, all of whom were living in the community, the VDRL test was positive. In 11 of these patients, the FTA-Abs also was positive. Only two BFP reactors were discovered in these 214 patients, an incidence of 0.9 percent. In one of these two patients, advanced rheumatoid arthritis was present. In the other, no cause for the BFP reaction was detected. Evidence of an actual past or present syphilitic infection was found in 11 pa-

TABLE 1.—*Characteristics of Patients in Whom VDRL Tests Were Positive*

Patient	*Sex*	*Age*	*Race*	*Primary Diagnoses*	*Serum Quant. VDRL*	*Serum FTA-Abs*	*Syphilis Previously Diagnosed*	*CSF*
1	♀	76	W	dementia	1:2	−	no	unobtainable
2	♂	80	W	depression	1:2	+	no	VDRL (−) FTA-Abs (−)
3	♀	65	B	paranoid psychosis with grandiosity	1:4	+	yes (inadequate Rx)	VDRL (+) FTA-Abs (+) pleocytosis
4	♂	85	W	depression	1:16	+	no	unobtainable
5	♀	84	W	paranoid psychosis with grandiosity	1:4	+	no	unobtainable
6	♀	74	W	depression	1:4	+	yes (inadequate Rx)	unobtainable
7	♀	72	W	paranoid psychosis with depression	1:2	+	yes (adequate Rx)	unobtainable
8	♂	68	W	(a) chronic obstructive pulmonary disease (b) paranoid personality	1:4	+	yes (adequate Rx)	unobtainable
9	♀	71	W	(a) dementia (b) depression	1:2	+	no	VDRL (−) FTA-Abs (−)
10	♀	75	W	dementia	1:2	+	yes (inadequate Rx)	unobtainable
11	♂	66	B	dementia	1:2	+	no	VDRL (−) FTA-Abs (+)
12	♀	76	W	depression	1:4	+	no	unobtainable
13	♀	70	W	(a) schizoid personality (b) rheumatoid arthritis	1:2	−	no	unobtainable

CSF = cerebrospinal fluid
FTA-Abs = fluorescent treponemal antibody absorption test
VDRL = Venereal Disease Research Laboratories (test)

tients, a "true positive" incidence of 5.1 percent for this population. In six of these patients, syphilis had not been detected previously, giving an effective discovery rate of 2.8 percent in the population screened. In three of the five previously detected cases, adequate antiluetic therapy had not been carried out.

Quantitative VDRL test titers were low or moderate (see Table 1). Among the FTA-Abs positive patients, titers were 1:2 in five patients, 1:4 in five patients and 1:16 in one patient. The titers of both BFP reactors were 1:2.

Definitive evaluation of the "true positive" patients was complicated both by the frequent reluctance of the patients to have diagnostic procedures done, as well as by the nature of our program as a screening agency rather than a provider of primary care. Of the nine patients with newly detected syphilis or previously detected syphilis inadequately treated, five patients either refused lumbar puncture, or their primary physicians elected to treat them as if they had neurosyphilis rather than "subject" them to lumbar puncture. These five patients were treated with 2.4 million units of benzathine penicillin G (Bicillin®) once a week for four weeks. In patients 2 and 9, findings on studies of cerebrospinal fluid (CSF) were within normal limits. In patient 11, a CSF VDRL test was negative and both protein and cell count were normal, but a CSF FTA-Abs was positive. In patient 3 there was evidence of active CNS syphilis with positive CNS VDRL, FTA-Abs and pleocytosis. This patient improved after treatment, but refused follow-up lumbar puncture.

Of note was the case of a 76-year-old woman, in whom a VDRL test had been negative three years earlier. The now positive VDRL test (1:4) and FTA-Abs indicated a recently acquired syphilitic infection in an elderly patient. She did report to being sexually active. Unfortunately, she refused lumbar puncture.

Discussion and Conclusion

The low rate of BFP reactors in this population is at variance with findings in those reports previously cited. One possible explanation may be the different settings in which patients were studied. Patients in institutions for the elderly[5,6] or admitted to a general hospital[7] may have had a higher incidence of various acute and chronic medical illnesses than did our patients, who were at least physically healthy enough to continue to live in the community. It is of interest, however, that in our small subgroup of patients in institutions (36), there were no BFP reactors.

In this population of elderly patients screened for psychiatric difficulties living in the community BFP reactors are rare, and age per se does not appear to predict an excessive number of BFP reactors. In fact, a positive serum VDRL test, a relatively frequent phenomenon in this population, usually indicates past or present syphilitic infection.

It appears important, therefore, to consider the possibility of syphilis in elderly patients with neuropsychiatric illness. Many elderly persons are sexually active, and primary syphilis knows no age barrier.[8] In a series of 210 patients treated for early syphilis between 1955 and 1962, 5.2 percent were older than 60 years of age.[9] Even if sexual activity has ceased, the occasionally prolonged latency of neurosyphilis can delay the clinical manifestations of syphilis acquired in earlier life; and as we have already noted in a few instances, inadequate earlier treatment may come to light.

Whether the cognitive, emotional and behavioral symptoms of some of these elderly patients was a result of central nervous system syphilis was difficult to determine, especially in this group of psychiatrically ill patients, most of whom resisted the procedures necessary for study of cerebrospinal fluid. Although the psychiatric symptoms in patients 3, 4, 5 and 6 improved after a course of penicillin, psychotropic medications and psychosocial interventions were parts of their therapeutic regimens, and may have been the effective treatment approaches. What is certain is that clinicians should not dismiss the possibility of syphilitic infection in this age group, and that a positive serum VDRL test must be evaluated as vigorously in an old patient as in a young one.

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Specialty Conference

Participants
BRENDAN CANNING, MD
RONALD M. KOBAYASHI, MD
CYNTHIA G. KAPLAN, MD
JAMES A. ROBB, MD

Taken from a Neurologic Clinicopathologic Conference held at the University Hospital, University of California, San Diego on August 29, 1975.

Refer to: Canning B, Kobayashi RM, Kaplan CG, et al: Progressive multifocal leukoencephalopathy—Neurologic Clinicopathologic Conference, University of California, San Diego, and University Hospital, San Diego (Specialty Conference). West J Med 125:364-369, Nov 1976

Progressive Multifocal Leukoencephalopathy

BRENDAN CANNING, MD:* A 76-year-old man was first admitted in December 1974 with complaint of progressive fatigue, easy bruising and a 40-pound weight loss over two to three months. On physical examination, pallor, scattered ecchymoses and hepatosplenomegaly were noted. There was impaired appreciation of vibratory sense, pin prick and touch below the knees; results of neurological examination were otherwise unremarkable. Laboratory studies gave the following values: hematocrit reading, 24 percent; platelet count, 35,000 to 58,000 per cu mm; leukocyte count, 138,000 per cu mm, with 98 percent mature lymphocytes. A diagnosis of chronic lymphocytic leukemia was made and treatment carried out with transfusion, administration of allopurinal for hyperuricemia and a two-month regimen of cyclophosphamide (Cytoxan®).

The patient was readmitted in January 1975 with an apparent infection on the floor of his mouth. This responded to administration of antibiotics and local treatment. Findings on lumbar puncture were normal.

The patient was first evaluated by the neurology service on June 4, 1975 for two to three months of poor balance and occasional falls. One month before, he had been briefly stunned but not knocked out from a fall. Since then he had become irascible. The patient said that he had not had headaches but that he had had difficulty with reading. He was alert, with normal speech and intact mental status. He had difficulty switching lines while reading a newspaper with either eye and with both eyes at the same time. Bilateral cataracts and macular change with visual acuity of 20/30 in the right eye and 20/60 in the left eye were present. Extraocular movements were normal, as was motor performance. Reflexes were normal except for absent ankle jerks bilaterally. Vibratory sense was absent below the knees. There was slight unsteadiness on heel to toe walking with a positive Romberg sign.

On July 9, 1975 the patient was admitted because of periods of confusion, increasing irritability with inappropriate behavior, and sleeping during the day. His wife stated his vision had deteriorated in the previous four weeks, and he had become unable to dress or feed himself in the preceding week. He became disoriented and could not find the bathroom. He was intermittently alert, oriented to person, place, date, but not time. Calculations such as serial subtraction of sevens were performed well and he remembered three of five objects after five minutes. Speech was clear and judgment appeared to be intact. He was unable to see well enough to read or write. He could not count fingers at 6 inches, but could distinguish light from dark. A left homonymous hemianopsia was present. The pupils were equal, reactive to light and accommodation. Fundi were normal. Extraocular movements were intact with mild nystagamus on lateral gaze. There was a left lower facial weakness with forehead sparing. Lower cranial nerves were intact. A mild to moderate left hemiparesis was present, with a left Babinski sign. Ankle jerks were absent bilaterally. Results of sensory examination were

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normal in the upper extremities but were inconsistent in the lower extremities. Gait was unsteady, and the patient was unable to tandem walk. The Romberg sign was positive.

The hematocrit reading was 38 percent; leukocyte count was 22,400 per cu mm, with 94 percent lymphocytes; platelet count was 47,000 per cu mm. A random blood glucose value was 152 mg per 100 ml. The blood urea nitrogen level was 43 mg and the creatinine level was 1.9 mg per 100 ml. Findings on studies of serum electrolytes, calcium, bilirubin, lactic dehydrogenase and alkaline phosphatase were all within normal limits. The serum cholesterol value was 174 mg and triglycerides were 163 mg per 100 ml. Findings on analysis of urine and on electrocardiogram were within normal limits. On an x-ray film of the skull, a small bone island was noted in the left parietal region. Brain scan showed normal flow with suggestion of increased uptake in the left parieto-occipital region (possibly in bone). On electroencephalogram there was dysrhythmia Grade I generalized, maximal in left temporal region.

The patient became intermittently resistive, agitated and confused; chlordiazepoxide and haloperidol were given. On the third hospital day, his sensorium was improved, and he could now read letters. On the fourth hospital day he fell out of bed and sustained a small laceration on the left occipital area. Results of neurological examination showed no changes. No fracture was seen on an x-ray film of the skull. On the fifth hospital day he was found to be lethargic but arousable, and had a stiff neck. He had a temperature of 100.8 to 102.3°F with Cheyne-Stokes respirations; on an x-ray film of the chest no acute changes were seen. Findings on studies of sputum showed many polymorphonuclear leukocytes and Gram-positive cocci. On lumbar puncture there was an opening pressure of 75 mm with initially clear fluid that subsequently became streaked with blood. In the first tube there were 1,700 erythrocytes and 60 leukocytes (all mononuclears). In the third tube there were 26,150 erythrocytes and 420 leukocytes (all mononuclears). The supernatant fluid was colorless. Protein was 51 mg per 100 ml and sugar 84 mg per 100 ml. Spinal fluid cultures were negative. With hydration, the fever subsided and the patient's condition improved without antibiotic therapy. On the sixth hospital day his temperature rose to 102°F. The patient became increasingly lethargic, but was able to follow two-part commands and repeat, and at one point was said to be alert. Lumbar puncture was repeated, and after several attempts bloody cerebrospinal fluid was obtained. In the second tube were 3,000 erythrocytes and 111 leukocytes (all mononuclears). The protein was 61 mg per 100 ml. On the eighth hospital day, his temperature rose to 104°F and the patient became hypotensive. Administration of penicillin and gentamicin was begun, but the patient died later that day.

Differential Diagnosis

RONALD M. KOBAYASHI, MD:* The illness in this 76-year-old man evolved in two phases. The first phase was recognized eight months before death when chronic lymphocytic leukemia was diagnosed. This diagnosis is straightforward and unequivocal.

The second phase of this illness was neurological and began four to six months after the diagnosis of chronic lymphocytic leukemia was made. The initial symptoms consisted of poor balance resulting in falls, behavioral change and some reading disability. The findings of decreased perception of vibration, pin prick and touch in the lower legs, absent ankle jerks, unsteady gait and positive Romberg's sign with normal motor power indicate the presence of a sensory polyneuropathy. The deficits of a sensory polyneuropathy may be partially compensated by visual cueing. In the presence of diminished visual acuity accompanied by cataracts and macular change, however, visual compensation may be impaired. This may be sufficient explanation for the poor balance and falls. In fact, diminished sensation in the legs was observed during the December 1974 admission, but the patient was apparently asymptomatic at that time. That is evidence suggestive of a progressive neuropathy. The possible explanations for this sensory polyneuropathy are relatively few. Uremia secondary to hyperuricemia is unlikely with a blood urea nitrogen level of only 43 mg per 100 ml. Random studies of blood glucose showed slightly elevated levels, but this does not necessarily indicate that the neuropathy was of diabetic origin. If the patient were alcoholic, this would be a possible cause. Neuropathies, either sensory or sensorimotor, are among the most common of paraneoplastic processes, or remote effect of carcinoma, especially with carcinoma of the lung.[1]

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In the absence of other documented causes, I am left with the possibility that the neuropathy is a remote effect of the underlying malignancy. Frequent falls are of particular concern in a thrombocytopenic patient, but his alertness and intact mental status are evidence against a chronic subdural hematoma that could either arise spontaneously or as a consequence of head trauma from a fall.

During the four weeks after the initial neurologic evaluation, the patient's condition progressively worsened and resulted in his final admission. The prominent symptoms may be summarized as progressive mental and personality deterioration accompanied by pronounced visual impairment. In the presence of normal pupillary responses and normal fundi, the localization of the bilateral blindness should be caudal to the lateral geniculate bodies and involve both sides. The left hemianopsia suggests more extensive involvement of the right visual pathway. The left hemiparesis with reflex asymmetry and a Babinski response along with the facial palsy of central origin are consistent with a subcortical lesion on the right. Fluctuating mental status is relatively common in patients with lesions of the nondominant hemisphere.

Laboratory tests of particular neurological interest are the skull x-ray, brain scan and electroencephalogram. If these show any abnormality at all, it was on the wrong side.

The lumbar puncture findings raise some important considerations. First, the indications are rather clear-cut because the presence of fever and nuchal rigidity suggest meningitis, although one examiner ascribed the rigidity to osteoarthritis. Patients with chronic lymphocytic leukemia carry a high risk of infection. The results obtained from the lumbar puncture, however, are more confusing than clarifying. The lumbar puncture was apparently traumatic since the fluid was initially clear and then became streaked with blood. This observation is corroborated by the rise in red blood cells from the first to the third tube. Intracranial bleeding in chronic lymphocytic leukemia is primarily subarachnoid and secondary to thrombocytopenia. If there had been major intracranial bleeding, the expected findings would include increased cerebrospinal fluid pressure, xanthochromia and elevation of the protein level. These findings are absent. Of more concern is the apparent increase of leukocytes for the amount of red cells present. Since bacterial, fungal or tuberculous infection should elevate the cerebrospinal fluid protein level and lower the glucose level (at least in bacterial infection), this appears unlikely. Are these mononuclear cells actually lymphocytes which are present in increased number due to his underlying leukemia? Cytology was not done, but might have been useful in this differential. The repeat spinal tap on the next day also appeared to be traumatic. It should be mentioned that spinal taps in patients with thrombocytopenia carry the risk of subdural or epidural hematoma at the puncture site and should be done only with clear indications and with great caution.[2] Following this evaluation, the patient made some unsustained improvement, became febrile and died on the eighth hospital day.

To summarize, the neurological problem was characterized by progressive mental change, pronounced bilateral visual impairment, left hemiparesis and left hemianopsia superimposed on chronic lymphocytic leukemia and sensory polyneuropathy. The disease involves both sides of the brain and is largely supratentorial in location. What disease process or processes are responsible? Are these manifestations related to his underlying leukemia or are they independent?

Of the unlikely considerations, I should briefly mention metabolic disorders, leukemic infiltration with or without hydrocephalus, infections, central pontine myelinolysis, limbic encephalitis, subdural hematoma and vascular disease. Metabolic disturbances such as hypercalcemia, hyponatremia, hypoglycemia, failure of the kidneys, liver or lung, and drug intoxications have either been excluded by normal laboratory values or are not adequate explanations for the neurologic features. Leukemic infiltration and meningeal implants usually occur with acute rather than chronic leukemia. The infiltrations cause mental changes in 80 percent and headaches in 50 percent of patients and have a very different spinal fluid profile consisting of elevated pressure, protein levels and cells, diminished glucose and positive cytology. Hydrocephalus may result from these meningeal implants. This condition appears unlikely. Bacterial and fungal infections, while occurring with greater frequency in chronic lymphocytic leukemia, are unlikely in view of the spinal fluid profile and negative cultures. Central nervous system bacterial infection in leukemia, moreover, is usually associated with leukopenia as indicated by a recent report from the Sloan Kettering Cancer Institute.[3] Viral encephalitis is far less frequent than bacte-

rial or fungal encephalitis. Central pontine myelinolysis occurs in malnourished alcoholics, but has also been reported with leukemia. Different clinical features are present consisting of quadriparesis, ocular palsies, pupillary abnormalities and bulbar signs. This diagnosis is unlikely. Limbic encephalitis is another paraneoplastic complication, and it characteristically produces memory impairment, dementia and seizures with a more insidious time course than seen in this patient.[4] Subdural hematoma is not usually associated with hemianopsia and often causes xanthochromia of the cerebrospinal fluid. Although the thrombocytopenia may be a predisposing condition, I doubt that a subdural hematoma was a significant factor.

The most difficult diagnosis to exclude is that of cerebral vascular disease. Against this diagnosis is a lack of predisposing conditions and concomitants, such as evidence of vascular disease in other organs, history of transient ischemic attacks or signs of carotid disease, hypertension, diabetes, or elevated cholesterol or triglycerides or both. Bilateral central retinal artery occlusion is unlikely to produce the visual loss without a history that the loss was sudden, and changes in the fundi would be expected. Furthermore, the temporal profile is not typical of cerebral vascular disease. It is possible that the left hemiparesis and hemianopsia occurred without the patient's awareness at any point in the month preceding his final admission because patients with nondominant hemisphere lesions may be unaware of the deficit. It may, therefore, not be possible to document the temporal profile. During the month following a stroke, however, electroencephalograms and brain scans would be expected to show the abnormality. Furthermore, bilateral lesions would be required to explain the visual symptoms and mental changes. If vascular in nature, the process is more likely multifocal emboli than thrombotic infarction, because the involvement is bilateral and asymmetrical. Findings on the neurological studies also do not support the presence of discrete large infarcts. If embolic, what is the source? Marantic or nonbacterial endocarditis is usually associated with adenocarcinomas. There is no evidence of emboli to other organs such as spleen, kidney or lung.

I favor the diagnosis of progressive multifocal leukoencephalopathy (PML), which is rare by contrast to vascular disease, but adheres to the

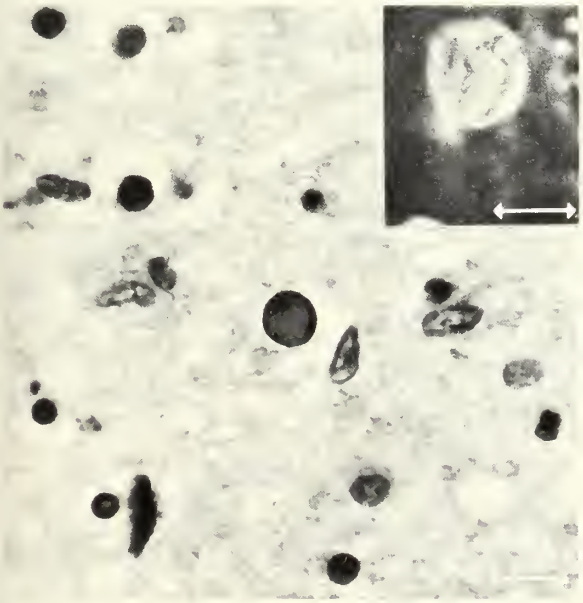

Figure 1.—Focus of demyelination in the parietal cortex. An affected oligodendrocyte with an enlarged nucleus is present in the center of the field. Tissue stained with H & E. Scale bar is 30 μm. The inset shows an affected oligodendrocyte that is positive for JC virions when examined by indirect immunofluorescence. The small bright objects are normal autofluorescence. The scale bar is 15 μm.

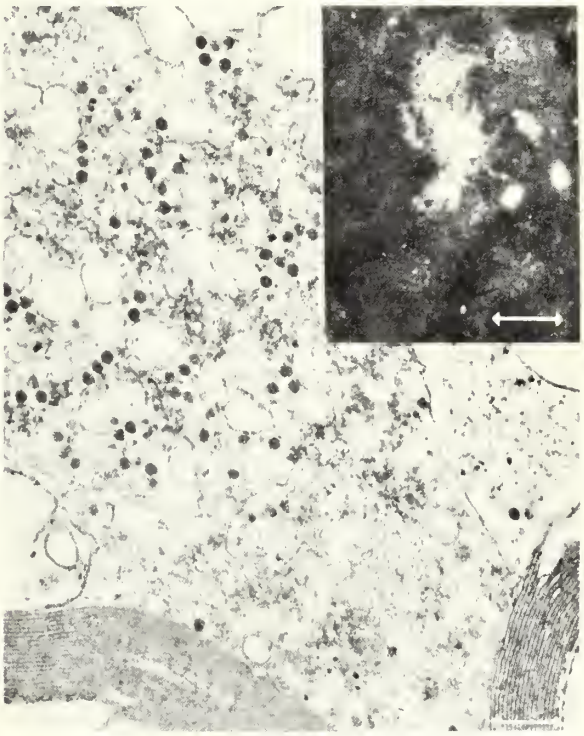

Figure 2.—Papovavirus in the cytoplasm of an affected oligodendrocyte. The scale bar is 200 nm. The inset shows that the virus in the cytoplasm of the affected oligodendrocytes is positively stained by antiserum to JC virions using indirect immunofluorescence. The scale bar is 30 μm and the small bright spots are autofluorescence.

principle of parsimony. This diagnosis adequately explains the clinical findings and course, and relates these to the underlying leukemia. The usual conditions for PML are met in this case. First, PML is usually associated with an underlying malignancy or chronic disease. Of these underlying diseases, chronic lymphocytic leukemia is second only to Hodgkin's disease, having been observed in 18 percent of the first 83 cases reviewed pathologically by Richardson.[5] Other cases of PML have been related to tuberculosis, sarcoidosis, systemic lupus erythematosis, renal transplantation and nontropical sprue. Second, this case is consistent with the clinical principles that in PML asymmetrical involvement is the rule and cerebral manifestations predominate, although brain stem, cerebellar and spinal involvement may occur. Typical initial manifestations are monoparesis or hemiparesis with altered mental state, personality changes and visual loss. As the disease progresses over its usual three to six month course, there is pronounced deterioration of mental function, vision and motor performance. It is to be emphasized that this is a diagnosis based on these characteristic clinical features. The laboratory studies, such as cerebrospinal fluid examination, brain scan and radiology offer only negative results. Findings on an electroencephalogram are usually abnormal, but in no way specific. The basic process appears to be caused by a papovavirus infection in immunodeficient patients.[6] The clinical diagnosis may be confirmed by biopsy study of the brain, utilizing light and electron microscopy, and by rapid immunofluorescence techniques.[6] Treatment with the antideoxyviral agents cytarabine and idoxiuridine has been unsuccessful except for a single case which remitted after treatment with cytarabine.[7]

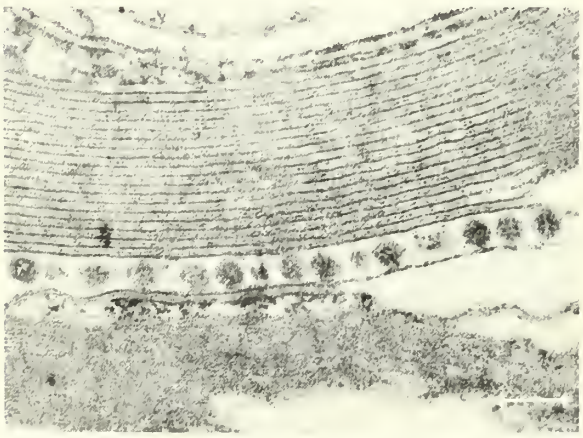

Figure 3.—Papovavirus in the extracellular space between myelin sheaths. The scale bar is 100 μm. The virus particles are approximately 35 nm in diameter.

My diagnoses are: (1) chronic lymphocytic leukemia; (2) progressive multifocal leukoencephalopathy; (3) sensory polyneuropathy, possibly with a paraneoplastic cause, and (4) terminal infection, either pneumonia or septicemia.

Pathological Features

CYNTHIA G. KAPLAN, MD:* An acute necrotizing pneumonia due to Escherichia coli and Staphylococcus aureus resulted in septicemia and the patient's death. Three pathologic entities were present in the brain: (1) chronic lymphocytic leukemia, (2) cystic infarct and (3) progressive multifocal leukoencephalopathy. Chronic lymphocytic leukemia of the brain was documented by diffuse perivascular cuffing with small lymphocytes having a relatively uniform, mature morphology. The brain parenchyma was not infiltrated. The meninges were free of cellular infiltrates. A small healed cystic infarct was present in the right putamen. The most important entity was progressive multifocal leukoencephalopathy. This disease was manifested morphologically by multiple asymmetrically located foci of demyelination with some axonal loss. These foci contained macrophages filled with myelin fragments, oligodendrocytes with enlarged circular nuclei (Figure 1) and astrocytes with enlarged bizarre nuclei. These foci were not related to blood vessels and did not contain any polymorphonuclear or mononuclear cellular infiltrates other than macrophages. These lesions were shown to be present in the frontal cortex, parietal cortex, left visual cortex, cerebellum, basal ganglia and medulla. Only mild atherosclerotic changes were present in the cerebral vessels. There was no cerebral edema, uncal or cerebellar herniation; meningitis; cortical trauma, or subdural or epidural hematoma formation. Peripheral nerves were normal.

Clinical Pathological Correlation

JAMES A. ROBB, MD:† The terminal event in this patient was septicemia secondary to acute necrotizing pneumonia caused by E. coli and S. aureus. Findings on examination of lymph nodes and bone marrow documented the chronic lymphocytic leukemia. The neurological problems in this patient

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were primarily related to the progressive multifocal leukoencephalopathy and not to the mild leukemic infiltrates in the cerebral perivascular spaces or to the small healed infarct in the right putamen. The progressive sensory polyneuropathy was most likely paraneoplastic, secondary to the chronic leukemia. Direct invasion of peripheral nerves by leukemic cells, however, was not observed in several independent sections of peripheral nerves.

Progressive multifocal leukoencephalopathy (PML) is still relatively rare and occurs in patients with an altered immune response, primarily in patients with lymphoma, iatrogenic immunosuppression and sarcoid. The cause of the disease is believed to be an activation of a latent infection by a human papovavirus called JC virus after the patient's initials from whom the first isolate was made[8] after ZuRhein observed the virus in the patient's brain by electron microscopy.[9] Humans are quite commonly infected at a young age (50 percent of 3 year olds have neutralizing antibody to JC virus) by this virus and another human papovavirus, BK virus. BK virus is not associated with PML. A simian virus 40 (SV40)-like virus was also isolated from a patient with PML.[10] These viruses probably remain associated with cells in various organs for life. JC virus appears to have a predilection for brain cells whereas BK virus has a predilection for kidney cells. BK virus has been isolated in the urine of renal transplant patients. In our case, a papovavirus was shown in the enlarged nuclei and cytoplasm (Figure 2) of affected oligodendrocytes. In these cells, virus replication occurred and killed the cell producing primary demyelination. No virus particles were observed in the affected astrocytes. The virus was identified as JC virus by indirect immunofluorescence using antisera supplied by Dr. Kenneth Takemoto of the National Institutes of Health. The infected oligodendrocytes stained positively with antiserum specific for JC virus, but did not stain with antiserum specific to BK virus or simian virus 40 (SV40) (Figures 1 and 2). Many of the affected oligodendrocytes had JC virus particles in their cytoplasm (Figure 2) indicating the beginning of cell lysis. Virus particles in the extracellular space were also present next to myelin sheaths (Figure 3).

The JC virus genome deoxyribonucleic acid (DNA) is thought to be incorporated into the DNA of the abnormal oligodendrocytes and astrocytes in the demyelinated foci and to function as if it were a cellular gene. The virus is activated to reproduce itself in at least some of the oligodendrocytes and kills them. The reasons for the virus activation are presently unknown, but are presumably due to the altered immune state of the patient. The virus, acting like a cellular gene in affected astrocytes, causes "transformation" of the astrocytes into bizarre cells with enlarged nuclei, but no virus is produced. These "transformed" astrocytes that do not produce virus are analogous to the cells that are "transformed" in test tubes by these viruses and other oncogenic papovaviruses such as SV40 and the mouse polyoma virus. The "transformed" astrocytes probably have the *in vivo* oncogenic potential of the JC virus although no direct evidence is yet available that the human papovaviruses produce cerebral tumors. SV40 causes cerebral tumors in young hamsters when inoculated intracerebrally. When JC virus infects cells in test tubes, a virus-coded antigen appears in the nuclei called tumor (T) antigen. This same antigen appears in the nuclei of cells in animal tumors produced by JC virus. This antigen is thought to regulate the growth of the tumor cells. The T antigen of JC, BK and SV40 viruses all cross-react immunologically. The nuclei in "transformed" astrocytes in our patient's parietal lobe, however, did not fluoresce when the cells were stained with antiserum specific for SV40 T antigen.

The interactions between JC virus infected cells and the human immune system producing progressive multifocal leukoencephalopathy, may provide a framework for understanding the possible roles of viruses in other central and peripheral nervous system diseases in humans such as multiple sclerosis, amyotrophic lateral sclerosis and subacute sclerosing panencephalitis.

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Refer to: Advances in the treatment of carcinoma of the breast —Medical Staff Conference, University of California, San Francisco. West J Med 125:370-378, Nov 1976

Advances in the Treatment of Carcinoma of the Breast

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *At Medical Grand Rounds this morning we are going to have a presentation on advances in the treatment of carcinoma of the breast.*

Case Summary

DR. BOZDECH:† The patient is a 47-year-old married woman who operates a beauty shop and is the mother of an 8-year-old son. She was referred to the University of California San Francisco Medical Center for a second consultative opinion regarding adjuvant chemotherapy for carcinoma of the breast. In January 1975, while in good health, she felt "lumpiness" in the upper outer aspect of her left breast and went to her gynecologist, who could not identify a specific lesion. However, in May 1975, on a repeat examination by her gynecologist, a firm mass with some skin fixation in the axillary tail of the left breast was found. The patient said there was no history of nipple discharge or bleeding. She had been taking birth control pills for about eight years and had regular but scant periods.

On October 5, 1975, she was examined by a consulting surgeon who confirmed the presence of a 2.5 by 3 cm firm mass with skin fixation in the upper outer quadrant of the left breast. He did not think the mass was fixed to muscle, and he felt no nodes in the left axilla. On October 8, 1975, a modified radical mastectomy was carried out. During the axillary dissection no evidence of enlarged nodes was apparent. A frozen section showed the presence of adenocarcinoma; a permanent section showed infiltrating ductal carcinoma, with 1 out of the 18 nodes dissected positive for disease. Further studies, which included a bone scan, bone survey and a right xeromammogram, gave negative findings. Results of liver function tests were within normal limits. From November to December 1975 radiotherapy to the lower axilla, internal mammary chain and left anterior chest wall was carried out. There was a total dose of 4,000 rads to the areas mentioned and concurrent radiation to the left supraclavicular and apical axilla to 4,500 rads, plus a boost to the internal mammary chain. The only complication from this therapy was some dermatitis with local edema.

In June 1976 the patient consulted an oncologist in her community about having chemotherapy and he advised her against it. On July 21, 1976, she came to the University of California Medical Center seeking corroboration of his opinion and there were no symptoms present at that time. Her past history was unremarkable, there had been no other operations or illnesses, and there was no

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Marek Bozdech, MD, Fellow in Hematology.

family history of breast cancer. Vital signs were normal; findings on physical examination were entirely unremarkable, with no evidence of local recurrence, adenopathy, hepatomegaly, bony tenderness or weight loss. Minimal laboratory studies done at that time gave findings within normal limits. The patient was advised, the referring physician was also notified and the patient went home to consider this advice.

DR. SMITH: *Thank you for that summary, with its somewhat Delphic implication. As you know, this is a very common problem in an area in which there has been tremendous controversy. We are very pleased to have Michael Friedman from the Cancer Research Institute to discuss this case and to tell us what advice was given and why.*

DR. FRIEDMAN:* This case represents a very perplexing medical, social and moral problem. The patient is an articulate, intelligent and attractive woman who is apparently free of all disease and who has received the benefits of multiple medical consultations. The radiotherapist who administered chest wall irradiation feels strongly that adjunctive chemotherapy is needed. She consulted an experienced oncologist who feels equally strongly that it would be inappropriate to give adjunctive chemotherapy at this time. Therefore, the patient came to our clinic for a further opinion and there was a further muddying of the waters. Rather than simply defending our advice to her, I would like to review some of the information from clinical and laboratory studies that helped us arrive at our decision. In retracing this thinking we can judge some of the virtues and vices of the various approaches to the adjuvant treatment of primary breast cancer that are used today.

We should begin with a brief review of some of the general aspects of tumor kinetics as described by Skipper.[1] The growth characteristics of a population of tumor cells varies with its mass. The growth of tumor masses can be described by a mathematical model (Figure 1); the general behavior of many tumors can be fitted to this Gompertzian curve. In very small tumors the mass of cells is small, individual cell growth is rapid, the doubling time is short and the fraction of growing cells is high. As tumors progressively enlarge, growth slows and a plateau state is reached. Small, early tumors grow rapidly (almost logarithmically); older larger tumors grow slowly.

*Michael A. Friedman, MD, Assistant Professor, Cancer Research Institute.

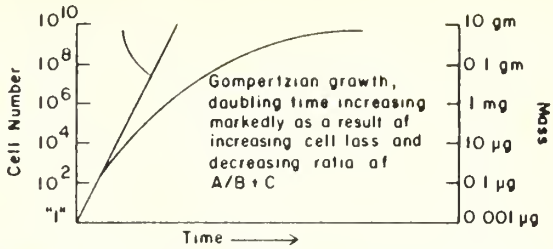

Figure 1.—The growth characteristics of populations of tumors. (Reproduced with permission from Cancer[1])

In order to describe the behavior of specific cellular components of tumors, we must consider a model proposed by Skipper and Zubrod.[2] They have arbitrarily allocated the tumor cells comprising a neoplasm into four compartments: A, B, C and D (Figure 2). Compartment A cells are those that are proliferating and are clonogenic. They are able to make new progeny and they divide rapidly. These are the predominant cells in small early tumors, those undergoing the log phase of growth. Compartment B cells are nonproliferating; they are not at the moment producing progeny, but they could initiate mitotic activity at any time. There is presumably free communication between cells of these two compartments (A and B). Larger tumors are composed mostly of B compartment cells. These cells often have a long T_{G1} (Gap 1) or are resting in the T_{G0} (Gap 0) phase of the cell cycle. Compartment C consists of cells that are nonclonogenic. They are viable and metabolically active, but unable to produce progeny. Compartment C is a repository for cells either from compartment A or B, but having once lost their proliferative ability these cells never regain it. Of course cells die and can be imagined to be in compartment D—of no further clinical interest.

The significance of this sort of an intellectual model is related to what it offers us clinically. Small tumors are mostly composed of proliferating cells (compartment A cells) and are sensitive to the drug and radiation therapy currently available. Larger tumors, made up of B compartment cells, represent a much more difficult clinical problem. These tumors are incompletely and inefficiently dealt with by conventional radiation therapy or chemotherapy. Certainly these modalities have some efficacy, but the cells are not nearly so sensitive as are the compartment A cells. Compartment C cells represent another sort of problem. These are cells that may not be truly malignant because they cannot produce. They may cause anatomic or architectural problems—a tu-

mor in the brain made up of compartment C cells, for example, would remain a problem—but this is an issue of practical rather than intellectual importance.

Utilizing these two concepts, Gompertzian growth kinetics and cellular compartments, we can imagine the biological path along which breast cancer proceeds. In an early tumor with rapid log phase growth, most cells are compartment A cells. These cells are rapidly proliferating and are very sensitive to the drugs and radiation therapy available. As the tumor becomes progressively larger, detectable by the relatively gross means at our disposal, it is composed primarily of compartment B cells. This tumor cell population is much more difficult to treat. Surgical operation remains the treatment approach that most efficiently removes compartment B cells and effectively deals with T_{G0} resting cells. After surgical "debulking" any remaining neoplastic cells become proliferating, compartment A cells. One of the most effective ways of perturbing cells to proliferate is simply to reduce the size of compartment B, thereby removing growth inhibition. One can imagine shifting back along the tumor growth curve into a phase where there is more rapid cell division.

Dr. Howard Skipper has raised some intriguing questions about malignancies in general, and breast cancer in particular.[1] To paraphrase these, first of all, after radical surgical procedures for breast cancer what fraction of patients still bear occult clonogenic tumor cells that can lead to recurrence? Clearly a recurrence of breast cancer leads invariably to death. Once disease is recurrent, the woman's fate is sealed. The only curative procedures at our disposal are surgical operation and, in rarer instances, radiation therapy for the primary tumor. Second, for those patients who bear some clonogenic tumor cell burden after operation, what is the number of these cells and what happens to them? Elegant investigations done at the time of operation have shown malignant-looking cells in peripheral venous blood which have been loosed at the time of surgical operation.[3] It is reasonable to imagine that if these cells have been loosed before operation you can also find them circulating in the peripheral blood. However, surgical operation is curative; therefore, even though these cells are being continually shed there must be mechanisms—possibly immunologic—that deal with these small numbers of cells and prevent them from becoming metastatic growths that kill the patient. Third, how can we deal with these clonogenic cells with the most effective available therapies? And finally, is it possible to utilize data on the natural history of breast cancer to identify a group of women who stand a much higher risk of recurrent disease postoperatively? That is, are there useful predictors which indicate which patient is likely or unlikely to have a local or distant recurrence?

We are all aware of the fact that breast cancer is a common problem in our community and it is probably increasing in frequency. There are approximately 75 new cases of breast cancer each year per 100,000 women and 27 women of that 100,000 will die of breast cancer.[4]

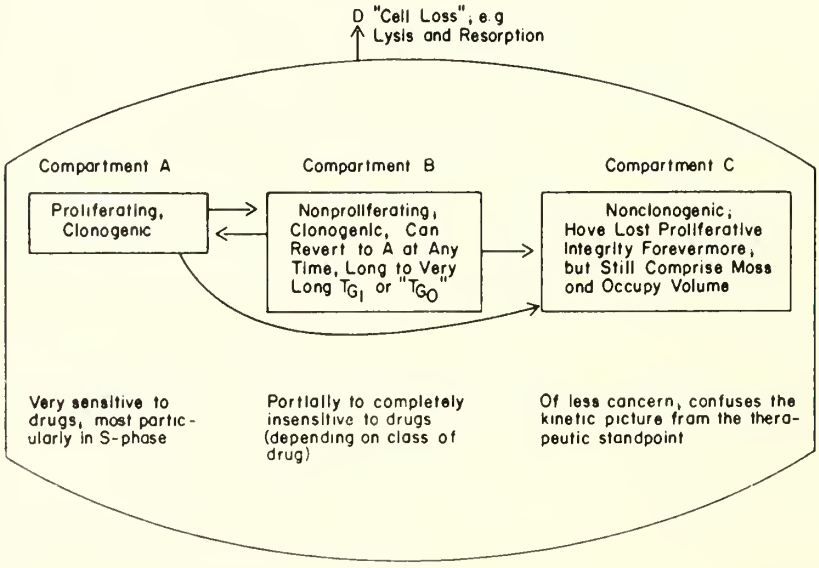

Figure 2.—Postulated populations of malignant cells within a tumor. (Reproduced with permission from Cancer[1])

The crucial natural history aspects of this disease are depicted graphically in Figure 3. Stage I disease is early breast cancer characterized by lesions that are 2 cm or less in the breast with no clinical axillary node involvement. Only 17 percent of all women with breast cancer are in this stage at the time of presentation. The prospect for five-year survival (this does not mean five-year cure) is relatively good; 85 percent of these women are alive five years later. But even in this group of women who have an excellent prognosis, a proportion will be dead in five years. Stage II disease is a much more common presentation. The tumors are larger, up to 5 cm, and there may

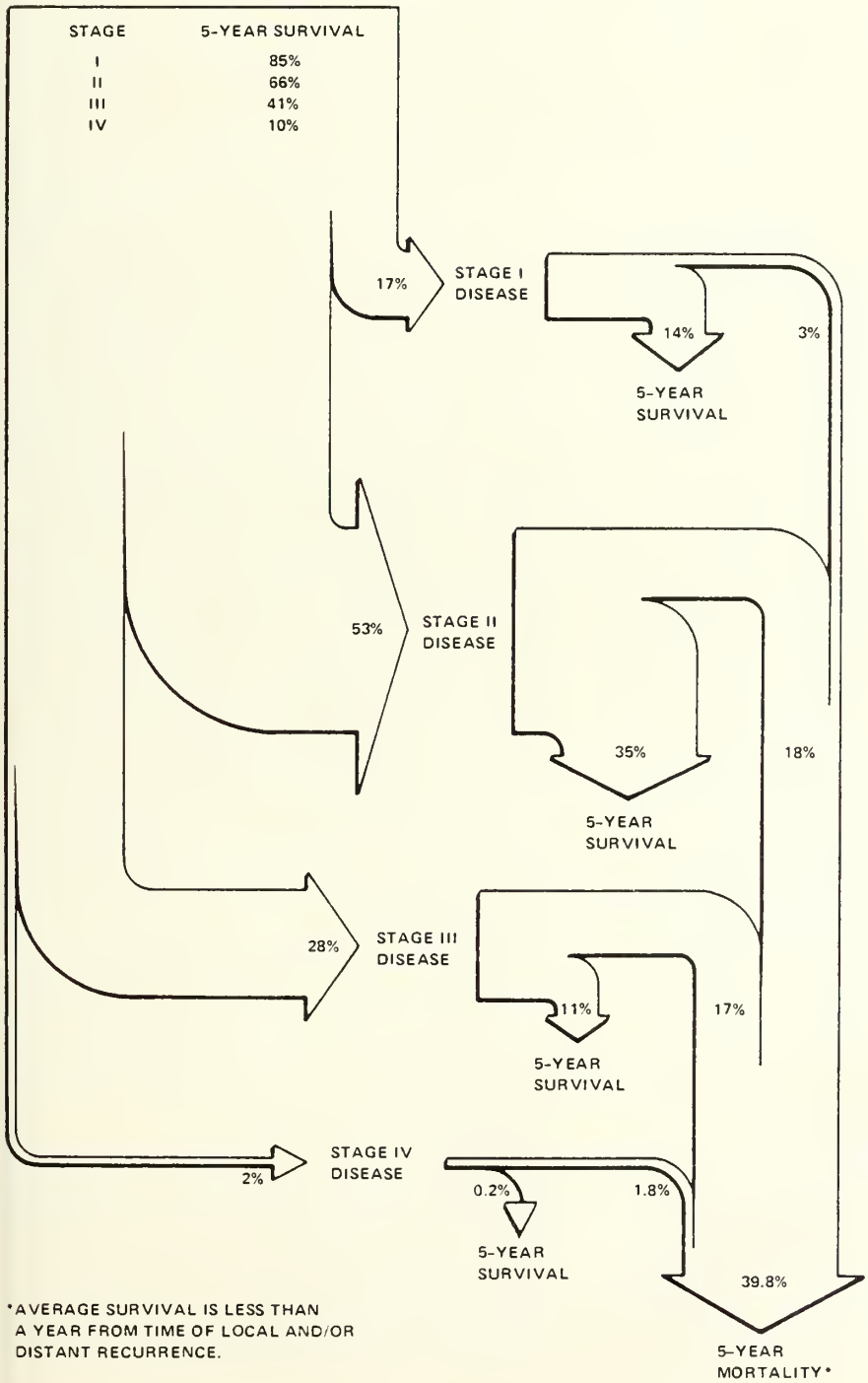

Figure 3.—Natural history of cancer of the breast in women.

TABLE 1.—*Recurrence Rate After Surgical Operation for Breast Cancer**

Nodal Status	*Time After Operation (Recurrence Rate in Percent)*		
	18 Months	*36 Months*	*60 Months*
1-3 positive	13	37	53
≥4 positive	52	68	80
All positive	33	53	67
Tumor >6.0 cm and 1-3 positive nodes	24	..	63
Tumor >6.0 cm and ≥4 positive nodes	62	..	94

*Based on information from Fisher and Slack.[5]

or may not be axillary node involvement on the same side. Again two out of three of the women do well, but a third of them die of breast cancer. Stage III disease is more advanced. The tumor is larger than 5 cm, most often the axillary contents are involved, and more than one out of two of these women still die of breast cancer (even with adequate surgical procedures on the breast). Stage IV disease is that which is metastatic at the time of operation and the five-year survival is low in this group of women. These figures indicate whether to expect a woman having a certain stage of breast cancer to live for five years with or without disease.

The patient we previously described has stage II disease. The primary lesion was modest in size, but one of 18 axillary lymph nodes was involved. Her chance of living five years is two out of three. But by the same token there is a one in three chance of recurrence of breast cancer and of death from it. It is always difficult to apply broad statistical trends to individual patients.

Of the 90,000 new cases of breast cancer each year, perhaps 40 to 50 percent of the women will have axillary nodes involved and this is the best, the simplest and the most important discriminant we have clinically. In one of his early studies, Fisher and his associates[5] asked the question: "If the axillary lymph nodes are involved after curative surgery, does the number of nodes involved make any difference in the recurrence rate?" Table 1 shows that when one to three axillary nodes are involved, 13 percent of the women have recurrences within a year and a half, increasing to almost 50 percent by five years. At ten years, the number is slightly greater. If more than four nodes are positive, a much more rapid recurrence pattern occurs. In half of the women there are recurrences at a year and a half, progressing to 80 percent by five years. The size of the primary tumor also is significant; in women with large primary tumors and more than four positive axillary nodes there is a recurrence rate of between 90 and 100 percent. Even if there are no axillary lymph nodes involved, in 5 percent of these women there will be a recurrence at 18 months. At five years, in 21 percent there is a recurrence, and by ten years in 25 percent of these women there is recurrent breast cancer. Thus, in the group of women who are at lowest risk, there is a one in four chance of recurrent disease developing.

Philosophically, the efficacy of surgical operation as a modality must be reevaluated. It certainly cures many women primarily, it gives us crucial information about the stage of the breast cancer, but we know that it may be insufficient therapy in perhaps 40 to 50 percent of all women. It is unlikely that any advance in surgical technique alone will improve the likelihood of disease-free survival. Since the introduction of the radical mastectomy by Halsted[6] in the latter part of the last century, the ability to deal with the primary tumor has been progressively improving. Surgeons are careful and competent in resecting local breast disease. The clinical problems of breast cancer, however, are of a more widespread nature. It is not the local disease that is difficult to control, it is the metastatic disease. Results of a clinical experiment have shown this clearly: Women having radical mastectomies were randomized postoperatively to receive radiation therapy to the chest wall or to receive nothing. Comparing their ultimate survival there was no difference between the two groups; that is, even though patients in whom both surgical operation and radiation therapy were done had fewer chest wall recurrences, their overall survival was unaffected. At similar rates both groups died of disseminated breast cancer.[7] These data intimate that breast cancer is a disseminated disease process and that it is not surgical failure that causes recurrences, it is the nature of the disease. Unless this disease is considered a systemic one from the beginning, attention is improperly focused on keeping the chest wall clear of disease while the patient dies.

Does this sort of thinking about the biology of breast cancer have implications for surgical studies? It certainly does. What the best surgical procedure may be for breast cancer has been a hotly contested issue, but this controversy is assuming less and less importance. The best operation depends on what the patient wants and what the surgeon wants. The classic principles of on-

cologic surgery hold true no matter what the setting. One must remove all of the primary tumor and one must have proper staging. Once those two demands are satisfied, it matters less what sort of surgical operation is done. There may be some instances in which a lumpectomy with axillary node dissection followed by radiation therapy or chemotherapy, or both, is equivalent to a radical or a modified radical mastectomy. I think that the type of newspapers one sees in grocery stores are going to have to search for another hot item of controversy because this one really has been exhausted. Surgical operation is an important modality in breast cancer, but it is insufficient in many cases. The logic is irrefutable, then, that adjunctive therapy with surgical operation should save more women, if we have effective adjunctive therapy.

Are there reasons to believe that there exist for adjunctive therapy animal model systems that would be applicable to humans? After a laboratory animal is inoculated in the thigh with a transplantable tumor, the tumor predictably metastasizes to the lung and kills the animal. If treated with chemotherapy the animal's survival time may be prolonged, but it will still die of disseminated disease. If the primary tumor is surgically removed, the animal will die, again of disseminated disease (because it had already metastasized at that point). But if the two manipulations are carried out together, that is if the recently inoculated tumor is resected and chemotherapy is administered, the animal can be cured.[8] This is a very persuasive model system that is of more than veterinary interest. A number of human malignant diseases: osteogenic sarcoma, embryonal rhabdomyosarcoma of childhood, Wilm's tumor of childhood and Burkitt's lymphoma have been successfully treated with this strategy. These are diseases in which it is abundantly clear that adjunctive therapy, that is surgical operation or radiation therapy plus effective chemotherapy, measurably adds to control of disease. This is an optimistic background for clinical trials in breast cancer.

In evaluating treatment of patients with breast cancer, several concerns must be addressed. First of all, systemic therapy should be contemplated for patients who are receiving "curative surgical procedures," for these procedures are not always curative and furthermore we can predict which patients are at added risk for having recurrent disease. The failures that occur represent breast cancer already disseminated at the time of surgical operation. Removing the tumor is necessary but insufficient therapy. Since it is impossible to detect occult disease after operation, we must treat blindly and systemically, and with the most effective agents possible. Second, the biologic and kinetic considerations mentioned earlier should be recalled. The contemporary approach has as its objective the destruction of all tumor cells by repetitive courses of chemotherapy. However, chemotherapy kills tumor cells at a rate that is best described as first order. That is, if a therapy kills 99 percent of a tumor the second course of that therapy, assuming that no drug resistance emerges, will kill 99 percent of the remaining cells, and so forth. A fixed proportion of cells is killed each time, not an absolute number. We can anticipate that by continued treatment, all cells could be ultimately eliminated. We know that advanced breast tumors contain cells that have relatively low growth fractions; they are at the plateau phase of their growth, they have long cycle times.[1] Many of the cells are nonclonogenic and therefore, are relatively insensitive to the therapies we use.

A third concern is whether we can provide sufficiently aggressive chemotherapy without endangering the patient's life. The goal is to kill 100 percent of the tumor; that is laudable and may be necessary. In an aggressive attempt to eradicate all tumor cells, we must realize that the drugs used are toxic and the side effects of these drugs are a well-recognized danger. There is a finite chance that a patient is going to die due to unpredictable drug toxicity. Such a mishap could result from a dose error on the part of the patient, on the part of the druggist or on the part of a prescribing physician. It could result from individual intolerance by that patient of a "usual" dose of chemotherapy. To have a patient die of toxicity would be a very distressing thing indeed, especially when a proportion of the women we are discussing are cured of breast cancer by surgical operation alone. It would be unacceptable to have many deaths secondary to an attempt to "rescue" even more of the women. Clearly, there are high risk groups of patients, women with large tumors or many axillary nodes involved, with whom these risks need to be negotiated. One out of five women with negative axillary nodes is fated to have recurrent breast cancer; even in women with the smallest risk of recurrence the question of whether

or not adjuvant therapy should be included needs to be considered.

We have some information from previous, older trials with adjuvant chemotherapy that may help us interpret the two new trials which I would like to discuss. In 1957 Dr. Fisher[9] began his first cooperative trials with breast cancer, and at that time he began studying cases of women who had primary resections for breast cancer which appeared to be curative. In his first study the methodology was a very simple one—postoperatively half the women were given a placebo and half were given an alkylating agent of known effectiveness, thiotepa. The patients were given the thiotepa only on the day of surgical operation and on the two subsequent days because it was thought that the dissemination of disease was an intraoperative event, and attempts were directed toward killing the cells circulating at the time of operation. At that time chemotherapy was thought to operate by zero order rather than first order kinetics, and it was presumed that a short course of chemotherapy could kill all the cells. Furthermore, little was known about the cell cycle of breast cancer cells; it was thought that they divided very rapidly and that a short course of therapy would be very appropriate.

Many of our concepts have subsequently changed, but even based on these serious methodologic flaws some important information came out of this trial. After a number of years the two groups were evaluated and when all the patients were pooled, there was no overall difference in rate of survival or recurrence. However, when a subpopulation of the treated group were extracted —in this case the premenopausal women who had four or more axillary nodes involved—there was a very significant advantage shown for that high risk subgroup. After many years (this study has been closed for more than ten years now), this group had still fared significantly better than the control group. It is not so noteworthy that this was a negative study. It is much more interesting that there were any positive results. Using chemotherapy in a less than optimal fashion, Fisher was still able to show some advantage for a highly selected group of patients. Since then, there have been several intraoperative and perioperative trials like this, utilizing alkylating agents or 5-fluorouracil. All of these studies have deficiencies in design, statistical analysis and methods of follow-up or staging.

In recent trials investigators have attempted to remedy some of these objections and have been cognizant of the following factors: The primary neoplasm and the regional nodes should be surgically removed because of the biological relationship between tumor size, host offense, and chemotherapy response. Patients are stratified according to the presence of histologically positive axillary nodes (associated with an increased incidence of recurrence). Chemotherapy should be started as quickly as possible after surgical operation, but continued for a long period, presumably to encompass many of the times for doubling of those cells. Prolonged adjunctive therapy has been very effective in other kinds of clinical human malignancy. First order cell kinetics apply to characterize the effective killing of cells by chemotherapy, and certainly we would like to include drugs that have proven efficacy in metastatic disease, presuming them to be more effective in earlier microscopic disease than in later disease. Additionally, chemotherapy should be administered intermittently to allow for as little immunosuppression as possible. Finally, the regimen should be safe, there should be no known long-term complications of the treatments, whatever toxicities there are should be minimal, predictable, reversible and not life-threatening. Treatments should be given to women as outpatients in order to interfere as little as possible with their lives.

TABLE 2.—*Clinical Trial of Prolonged Therapy with L-phenylalanine Mustard (L-Pam) as an Adjuvant to Surgical Operation in Breast Cancer**

Age 49		*Age 50-75*	
L-PAM	PLACEBO	L-PAM	PLACEBO
0.15 mg/kg/d P.O. × 5 Q 6 weeks		0.15 mg/kg/d P.O. × 5 Q 6 weeks	

*Based on information from Fisher B, Carbone P, Economou SG, et al.[10]

The first study I would like to describe in some detail is a more recent study of Dr. Fisher's[10] which utilized L-phenylalanine mustard (L-Pam®) as the chemotherapeutic adjuvant (Table 2). Women were divided into premenopausal and postmenopausal age groups (none were older than 75) and were randomized to receive either a placebo or L-phenylalanine mustard. The dosage was 0.15 mg per kg of body weight per day for five days, given every six weeks, for a total time of 18 months. These patients had no evidence of metastatic disease at the time of surgical operation. The study was begun in September

1972; it was terminated in January 1975, and the statistical analysis is still being done. During this period about 400 patients were randomized in the trial and in the most recently published data about 150 patients in each arm of the protocol were evaluated. In general the toxicity was infrequent and mild (only 10 percent of those administered doses). Leukopenia was infrequently noted. A third of the women who received the L-Pam had nausea and vomiting, but 11 percent of the placebo-treated women had the same symptoms. Most of the women felt that it was a very tolerable program. In the first published report of this data, there was a significant benefit for the L-phenylalanine mustard treated group. An overall comparison of the placebo groups and the L-phenylalanine mustard groups showed that treatment in 22 percent of the placebo group and in 10 percent of the L-Pam group had failed. A separate analysis of postmenopausal women showed a statistically significant difference at the 0.01 level. No statistical significance in the premenopausal control group was shown, but there was a trend favoring better control of disease for those women in the premenopausal group who were treated with L-phenylalanine mustard.

More recent evaluations of these data have been made (follow-up studies have been done on some of the women for more than five years), and unpublished reports substantiate the preliminary data for the postmenopausal group. Of all the L-phenylalanine mustard treated group, treatment failed in 17 percent compared with 25 percent for the placebo group. Dividing these groups into premenopausal and postmenopausal women, the failure rate for the premenopausal placebo group was 30 percent and for the L-phenylalanine mustard group 11 percent ($p<.001$). For postmenopausal women the placebo had a 19 percent failure rate and L-phenylalanine mustard a 23 percent failure rate. One possible conclusion is that use of L-Pam is ineffective in preventing malignant recurrence. However, L-phenylalanine mustard has a real impact on this disease, and one might presume that for premenopausal women this drug as a single agent is appropriate therapy for high risk groups. Based on these data L-Pam appears to be inappropriate therapy for postmenopausal patients. These data represent large numbers of patients from many institutions and are carefully handled; but breast cancer is a chronic malignant disease and, as such, evaluation at two or even five years may be insufficient. Full analyses at 10, 15 and 20 years must be made before we can draw definitive conclusions. This analysis of the data may comfort those who criticized this National Surgical Adjuvant Breast Program (NSABP) study as being prematurely published. There is an intellectual difficulty in deciding when a study is ripe for evaluation and publication, and when data should be distributed to the general medical community for their use.

TABLE 3.—*National Cancer Institute Milan, Italy Breast Cancer Adjuvant Study.* CMF is abbreviation for cyclophosphamide (Cytoxan®) methotrexate and 5-fluorouracil*

SURGERY With Positive Lymph Nodes, 2-4 Weeks	
"CMF"	NO FURTHER TREATMMENT
Cytoxan®, 100 mg/m² P.O. day 1-14	
5-fluorouracil 600 mg/m² } I.V. days 1 & 8 Methotrexate 40 mg/m² } I.V. days 1 & 8	
12 courses given at 4 week intervals	

*Based on information from Bonadonna G, Brusamolino E, Valagussa P, et al.[11]

The other major study that demands our attention is that of Bonadonna and his associates[11] at the National Cancer Institute of Milan. The study is similar to the NSABP trial; stratification was based on menopausal age and nodal involvement. In all patients curative breast surgical operation was done (axillary nodes were involved in all patients), half of the group received combination chemotherapy, the other half nothing further. CMF chemotherapy (a combination of three drugs: cytoxan, methotrexate and 5-fluorouracil) was used in this study. This is a therapy of known efficacy in women with metastatic breast cancer. It is more aggressive than single agent L-Pam therapy (and one might expect it to be *a priori* several fold more effective). It is associated with a 60 percent response rate in women with metastatic disease, in contrast to L-phenylalanine mustard which has a 20 percent response rate. Table 3 shows Bonadonna's intermittent schedule of therapy; pulses are given in four week cycles for 12 months.

L-Phenylalanine mustard was employed in the NSABP trial because the investigators did not want to expose patients to excessive toxicity. L-Pam can be given easily and safely. Patients taking this drug usually do not experience cystitis or alopecia. The toxicities encountered in Bonadonna's study were generally mild. Myelosuppression was noted in about half the patients, and conjunctivitis in

20 percent of the patients. There were no life-threatening toxicities and no toxic deaths occurred. Clearly, CMF chemotherapy is more toxic than use of L-Pam and the question is, "Was that extra toxicity therapeutically worth it?" An unpublished update of the information of this study indicates that use of CMF appears to be strikingly beneficial. The study has been in progress for only three years, but approximately 30 percent of both control premenopausal and postmenopausal women have had recurrences. By contrast, in the CMP-treated premenopausal women there has been an 8 percent failure rate. In the CMF-treated postmenopausal women, 15 percent have had recurrences. Both groups are highly different statistically. Apparently both the premenopausal and the postmenopausal women benefit from therapy. To date there do not seem to be any peculiar aspects of the recurrence patterns for either the CMF or control treated groups. In neither the CMF nor the L-Pam trial has there been any increased incidence of a second malignant disease, but of course it is premature to draw a definite conclusion from that datum. Most women find adjuvant chemotherapy to be tolerable, and the improvement in disease-free survival is dramatic.

It is possible that the magnitude of these differences will not persist at five- and ten-year analyses, but it seems likely that significant benefit will be evident. Adjuvant chemotherapy makes an important impact upon the natural history of breast cancer—a disease that otherwise has proved to be ultimately fatal. These preliminary reports are persuasive and satisfying.

In summary, there are several conclusions that can be drawn from this information:

- Arguments concerning the relative merits of different surgical procedures for breast cancer have become less engaging. It is apparent that both local and systemic approaches are necessary for complete therapy.
- Careful clinical trials will be needed to evaluate newer methods of dealing with local disease (surgical and radiation therapy techniques) and systemic disease (different combinations of chemotherapy and hormonal therapies varying dose, schedule and duration of treatment).
- As systemic therapy becomes more effective, perhaps less radical surgical operation will be equivalent to more radical procedures.
- Once the short- and long-term toxicities of adjuvant chemotherapy can be assessed (and no unacceptable toxicity is detectable), patients with negative axillary nodes should be treated with adjuvant therapy to attempt to improve their known 25 percent failure rate at ten years.

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Important Advances in Clinical Medicine

Epitomes of Progress—Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Orthopedics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Ankle Joint Replacement

IN THE PAST ankle arthroplasty was not considered necessary, largely because of the minimal disability associated with arthrodesis. However with the advent of new materials and the successful replacement of other joints, several devices have been developed for the ankle which have provided very good early results. The presently available devices are either stainless steel or cobalt-chromium-molybdenum alloy and ultra-high density polyethylene. They are cemented in place with methylmethacrylate.

Results to date suggest good pain relief, and increased motion may be anticipated in most patients.

For arthritic patients with multiple joint involvement, total ankle arthroplasty warrants consideration after several unsuccessful attempts have been made to achieve arthrodesis and when prolonged immobilization is undesirable. It is considered contraindicated following infection, in the presence of muscle weakness and neuropathic joints, and when a solid ankle arthrodesis already exists.

THEODORE WAUGH, MD

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Prevention of Venous Thromboembolism in Orthopedic Patients

ORTHOPEDIC PATIENTS, especially those with hip replacement or hip fracture, are at especially high risk for venous thromboembolism because of the trauma of necessary surgical operation followed by variable periods of rest in bed. However, because of the unique problem of persistent bleeding bone after operation and after fracture, it is impossible to apply the same prophylactic and

therapeutic regimens to orthopedic patients as to nonorthopedic patients without seriously weighing the risks of a dangerous increase in hemorrhage.

Many studies on the prevention of thromboembolism have been published during the last ten years—often with conflicting findings. Most deal with the incidence of deep vein thrombosis rather than the incidence of pulmonary embolism, yet venous thrombosis alone is of relatively minor consequence—its major importance is its relationship to the larger problem of pulmonary embolism. This relationship is still not fully understood.

The largest study on thromboembolism is the recently published international multicenter trial involving more than 4,000 general surgical patients, including 156 patients with total hip replacement. Its findings show an incidence of 0.7 percent fatal pulmonary embolism in patients receiving *no* prophylactic treatment. The incidence of fatal pulmonary embolism was reduced to 0.02 percent when subcutaneous heparin was given in the following way: 5,000 units every eight hours beginning two hours preoperatively and continuing for seven days or until the patient was ambulatory. However, there were *no* patients with acute fracture included in the multicenter trial, apparently for fear of hemorrhagic complications from the heparin. The patients undergoing total hip replacement who received heparin required 300 ml more blood than the untreated controls, and there was a slightly increased incidence of wound hematoma in the treated group as a whole.

These results are countered by those in a much smaller study which dealt exclusively with patients undergoing total hip replacement. Here it was shown that warfarin, low molecular weight dextran and aspirin were equally effective and all were superior to low dose subcutaneous heparin in decreasing the number of postoperative venous thrombi. With aspirin there was the added benefit of significantly fewer bleeding complications than with warfarin. The aspirin dosage schedule was a minimum of 600 mg the day before operation and postoperatively a minimum of 600 mg orally twice a day or 1,200 mg rectally twice a day until the patient was fully ambulatory and ready for discharge. The drug was discontinued abruptly at discharge.

Another modality now receiving attention is intraoperative intermittent calf compression. One attempt to assess the possible benefits of adding low dose heparin to the technique of intermittent calf compression found that in 84 general surgical patients the prevention of deep vein thrombosis achieved by calf compression alone was not enhanced by the addition of low dose heparin.

The complete answer to prevention of pulmonary embolism is still elusive. At present, intraoperative mechanical intermittent calf compression, early postoperative ambulation and preoperative and postoperative aspirin prophylaxis have been shown to be effective in decreasing the incidence of thromboembolism in orthopedic patients without adding significant risks of hemorrhage.

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Tarsal Tunnel Syndrome

TARSAL TUNNEL SYNDROME is somewhat analogous to the carpal tunnel syndrome. It results from compression of the posterior tibial nerve within the tarsal canal. The tarsal tunnel lies behind the medial malleolus.

A patient with tarsal tunnel syndrome usually has complaint of burning pain in the plantar aspect of the foot, often in the metatarsal area. Occasionally the patient will note pain radiating up the medial side of the calf. The pain often is aggravated by activities and relieved somewhat by rest. Some patients, however, state that they have burning in their feet while in bed at night.

The onset of the syndrome usually is slow and insidious. In about half of such patients there is a history of some type of trauma.

Findings on physical examination will include a positive Tinel's sign over the area of the tarsal tunnel. The patient often will note that tapping the tarsal tunnel causes radiation of pain into the foot along the distribution of the medial or lateral plantar nerve. It is unusual to find any consistent motor weakness within the foot and only occasionally is there a sensory deficit.

The diagnosis of tarsal tunnel syndrome should be confirmed by electrodiagnostic studies. The studies should consist of nerve conduction times,

particularly the terminal latency of the medial plantar nerve to the abductor hallucis and the lateral plantar nerve to the abductor digiti quinti muscle. It should be emphasized that the latency period to both muscles should be determined since the syndrome may involve only one branch of the nerve. Electromyography also should be done to locate abnormal potentials (fibrillations). Both the abductor hallucis and abductor digiti quinti muscles again should be sampled.

When the diagnosis has been made and the clinical symptoms warrant it, surgical exploration with decompression of the tarsal canal and neurolysis of the posterior tibial nerve and its terminal branches should be carried out. In the decompression of the tarsal canal, extreme care must be taken not to disrupt the medial calcaneal branch which supplies sensation to the medial side of the heel.

In my experience there has been complete relief of symptoms in 80 percent of patients with this approach.

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Compartment Syndromes of the Leg

COMPARTMENT SYNDROMES of the leg are recognized as resulting from an increasing number of diseases. Any mechanism that increases tissue pressure and decreases nutritional perfusion will reduce the microcirculation and may lead into a vicious circle resulting in ischemic necrosis. The anterior, lateral and deep posterior compartments of the leg are particularly vulnerable to such a process due to their confinement between bones and strong fascia. The superficial posterior compartment also may be involved particularly in crushing injuries.

Originally, clinical compartment syndromes were described as *Group I, idiopathic,* occurring most commonly in poorly conditioned persons subjected to great stress, such as young military recruits; and *Group II, traumatic,* associated with fractures and crushing injuries.

To this has been added *Group III, vascular,* associated with primary arterial or venous injury, or both. Group III now includes arterial perfusion which may be required as in open heart surgery and vascular compromise associated with tibial osteotomies.

In addition is *Group IV, miscellaneous,* which includes prolonged abnormal recumbent posture during drug induced stupor, snake bite, nephrosis, eclampsia, epilepsy, lumbar sympathectomy, disc surgery for low lumbar herniated nucleus pulposus, repair of muscle hernias and bracing.

Both acute and chronic forms of compartment syndromes do occur and usually require the same treatment unless foot drop has been complete for 10 to 12 hours. The simple anterior and lateral fasciotomy from the anterior approach is indicated if the anterior and lateral compartments only are involved but with fibulectomy and multiple fascial releases through its perostum if the posterior compartments are also involved. Early surgical release of compartment pressure is essential before irreversible muscle and nerve changes occur if satisfactory recovery is to result.

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Blood Loss in Fractures of the Pelvis

MAJOR FRACTURES of the pelvis can cause life-threatening hemorrhage. The magnitude of blood loss is usually underestimated. Polytrauma is the rule, confusing the estimation of volume deficit and rate of depletion. Exsanguination under observation can be prevented only by very aggressive management.

A patient with a major arterial injury is seldom seen, but injuries to the small arteries can cause dangerously persistent bleeding. Because of abundant collaterals, hypogastric artery ligation has not been shown to be uniformly successful. Selective arteriography can help locate the injured vessel and may allow therapeutic clot or muscle embolization, or identify the site for ligation. However, most of the bleeding is of venous origin, and even with large vein laceration will subside with general measures and adequate immobilization. Since the pelvic fractures associated with hemorrhage are unstable, it is imperative that lower extremity traction be instituted promptly.

A pelvic sling may be useful, but complicates abdominal evaluation and nursing care.

Prompt central venous catheterization will establish a large-bore channel for administration of blood and fluids, monitor the response of the heart to massive loading and provide a reliable route for medications. A large lumened catheter can also be placed in the opposite upper extremity or in the subclavian or external jugular veins. Micropore blood filters are necessary and lower extremity routes should be avoided.

If there is no gross blood at the urethra and examination does not contraindicate, retention-bag catheterization of the bladder will allow monitoring of urine quantity and quality. (Rectal examination should be done in men to be certain the prostate is not "floating"—which presumptively indicates transection of the membraneous urethra.) With gross blood, a contrast urethrogram must be done and a cystogram completed if the urethra is intact. Microscopic hematuria is an indication for excretory urography. Baseline arterial blood gas determinations are desirable because of the frequency of respiratory distress syndrome.

Major fractures of the pelvis will require blood replacement of a minimum of 25 percent and a maximum of all the patient's blood volume. For a patient in hypovolemic shock, therefore, at least eight units of whole blood will have to be available if resuscitation is to be successful.

TILLMAN M. MOORE, MD

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EDITORIALS

A BICENTENNIAL EDITORIAL ESSAY

A Broader Knowledge Base for Medicine

For a hundred years or so the focus of medicine—and its knowledge base—has centered increasingly on medicine as a rational science primarily concerned with how the human body works and on the care, treatment and prevention of what might be called the more or less mechanical malfunctions of the human organism. Considerably less attention has been given to the function and malfunction of the whole person, although lip service was paid to this approach by medical science, and many physicians continued to be very much concerned with it. But human behavior, particularly emotional behavior, and its malfunctions can often be more irrational than rational, and rational science by its very nature has tended to reject whatever is irrational, much as organic tissue will reject a substance foreign to it. As American medicine enters the third century of the nation's history it seems important to consider the impact of this, and also some of the effects of human interdependence within the closed biosphere, and the governance of this interdependence. All of these relate to the knowledge base that will be required of medicine in the future.

There are many signs that rational scientific medicine, as it has developed so far, may be falling short of both public and professional expectations for it. The public seems to be turning more openly to alternative systems of care. For example, acupuncture is being widely sought, chiropracty has been given new acceptance and standing in government programs, and there is increasing reference to something called holistic medicine. And on the professional side such things as the value of a routine physical examination and even some surgical procedures are being questioned by physicians themselves. Perhaps scientific medicine was oversold. In any case it does not seem to be able to do all that it claimed for itself or all that was claimed for it, although there surely have been notable achievements. The bottom line, to use a current expression, is to what extent there is value received for the dollars spent for medical science and health care, and here it appears that the gains in better health, greater well-being and increased quality of life have failed to match the rapidly rising costs. The result is some disillusionment and more supervision and direction of expenditures for research in medicine and for medical education and patient care.

It seems that medicine may have lost something in its absorption with rational science. Perhaps what was lost is the recognition that medicine is and always must be something more than a precise science. Medicine deals with human beings, and human behavior is not always rational in terms of scientific protocol. Many scientifically trained physicians have been surprised to discover the extent to which patients fail to follow their directions or advice, and on a national scale the Surgeon General has found much the same thing in his ten-year all-out campaign against cigarette smoking. There is an obvious need to take more account of irrational as well as rational behavior in healthy persons as well as sick ones. The behavioral sciences need somehow to become a more integral part of the knowledge base for medicine. Fortunately this has begun to occur, and it is likely that medicine will contribute as much to the behavioral sciences as it receives from them, as has happened to so many disciplines that have become adjunct to medicine in recent years.

But something else is going on that seems certain to extend the knowledge base of medicine even further. Physicians increasingly find themselves at the central point or interface where health, well-being or quality of life is or is not achieved by persons who must live in increasing interdependence with an ever more complex social and technological environment. This adds new dimensions to medicine. Health, well-being and quality of life—or the lack of them—all depend upon the individual person and the person's environment, and the interaction between them. A physician therefore must not only have some knowledge of the person and of human behavior, but also some awareness of the characteristics of the environment and an understanding of the re-

lationships of persons to their environments. This requires something more than a traditional working knowledge of what we now think of as scientific medicine. Further, human interdependence with respect to health, well-being and quality of life in the closed biosphere will inevitably become worldwide, and this will just as surely give rise to some form of governance or ordering of this interdependence. Some kind of system will emerge which will have health and well-being in an interdependent society as its focus. This system will somehow have to respond to the rationalities of medical sciences as these become established and the irrationalities as well as the rationalities of human behavior in relationship to the realities of social interdependence within the closed biosphere. There are those who say that all this is beyond the scope of medicine, but one wonders if this can be so. Medicine is the authoritative profession to determine what is health and what unhealth, and for unhealth (which is always a function of persons) to determine what is wrong, what is likely to happen and what can be done about it. An adequate knowledge base is needed to carry out this function. It would appear, therefore, that increasing human interdependence will demand still more of physicians and of medicine in new dimensions of the social as well as the behavioral sciences.

There is considerable to suggest that a start is already being made toward creating the broader knowledge base that will be needed for medicine. So far the effort seems spotty with some behavioral science finding its way into the medical school curriculum, and with some physicians who have entered the social, economic and political fray in behalf of medicine, that is physicians and patients, beginning to acquire some knowledge and skills in the general area of the social sciences. But much more will be necessary to incorporate needed new disciplines and skills into the research, education and practice of medicine.

To conclude, some years ago the Committee on the Role of Medicine in Society of the California Medical Association found the essential functions of physicians to be the following:

1. To render authoritative opinions concerning health with respect to (a) what is wrong, (b) what is probably going to happen, (c) what can be done about it.

2. To participate in decision making at all levels of health care.

3. To perform procedures and services as (a) problem solver, (b) manager, (c) skilled technician, (d) teacher or advisor, (e) advocate.

If these are indeed the essential functions of physicians in an increasingly interdependent world where health, well-being and quality of life are being sought by all, the knowledge base for medicine must be broadened sufficiently to be adequate to the task. Today, as America enters its third century, it is time for medicine to prepare for what are and will be some of the medical problems the nation will face in the century ahead.

—MSMW

Aspiration Pneumonitis — A Continuing Problem

As I WRITE these comments, I have just been consulted concerning a patient with severe aspiration pneumonitis. He will almost certainly die. The aspiration occurred in a very predictable fashion according to the article by Ruggera and Taylor that appears elsewhere in this issue. Yet this tragedy would almost certainly not have been avoided if the article had appeared in an earlier issue or if the anesthetization of this unfortunate patient had been carried out differently. The article reports nothing not reported before. As the references quoted attest, the problem is old and well recognized. There is no paucity of prophylactic procedures and the warning signs are plentiful. But what may be a common component of this syndrome is not mentioned in the list of articles referred to—a failure of those managing anesthesia to heed the warnings.

Pulmonary aspiration is a problem not restricted to operating rooms. It can occur whenever patients' reflexes and awareness are obtunded, and one hopes the word "anesthesia" in the title of the present article will not unduly limit the audience. Trauma, drug poisoning, stroke, diabetic coma, epilepsy and other similar conditions threaten patients with this unhappy situation.

Aspiration must not be a rare occurrence judging from the frequency of review articles. Certainly the message is not a complex one. Uncon-

scious people are unable to protect their airways and therefore those who care for such persons must provide the protection. This is a demanding responsibility and has resulted in many rules and procedures designed to minimize or prevent occurrence of aspiration pneumonitis. The rules demonstrate once again that good medical care, like virtue and respect, cannot be legislated.

As noted, the Ruggera and Taylor article is a review, and it presents no new information. Nonetheless, one could quarrel with the authors' uncontroversial presentation of some controversial matters, such as the role of steroids in treatment, the ineffectiveness or harmfulness of saline lavage, the degree of effectiveness of prophylactic gastric alkalization and the importance of atropine. These points are probably of limited importance, however, if proper management and awareness can be accomplished.

Why does aspiration pneumonitis persist in the presence of repeated warnings and development of several methods effective in prevention? Why does it still occur where trained personnel administer anesthesia? These rhetorical questions defy precise answer but do promote speculation. The incidence of this problem has almost certainly reduced sharply in recent decades. In many institutions, it is a rare occurrence in spite of an increasing number of opportunities for it to happen. The repeated reviews and warnings have been effective.

There is reason to believe that a most important factor related to incidence of this complication still is lack of expertise in management. For example, it is possible that the prevalence of the problem in obstetrical patients is as much due to poor coverage of obstetrical anesthesia as to factors particular to such patients. Some of the preventive measures—such as awake untubation and rapid induction techniques—are dependent on at least a modicum of operator skill and may therefore be inadequately accomplished or actually avoided by those less expert. The less conscientious may be lulled into a state of some complacency by the *almost* routine successful induction.

It is to be hoped that awareness of the problem will increase, for this will provide effective protective action. No additional methods are in fact necessary—if we use what we have.

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Treating Breast Carcinoma

THE SUBJECT of this month's Medical Staff Conference is advances in the treatment of carcinoma of the breast. Also in this issue are two articles dealing with breast reconstruction after surgical operation for breast cancer.

Breast cancer is a disease that currently is highly visible to the public. In both the printed press and the electronic media, reports abound about controversies and exciting results related to breast cancer in such areas as screening, detection, treatment and rehabilitation. In the 80 years since Halsted first described radical mastectomy, the treatment of breast cancer has remained a subject of strong controversy and weak data. Diverse proposals of new therapeutic regimens have been received with the often justified criticism that the population under survey was unrepresentative because of excessive selectivity and that findings were nonreproducible because of unsatisfactory examination, improper because of defective classification or insignificant because of small numbers.

Today the new exciting development is the adjuvant treatment with drugs of women after mastectomy. The hypothesis behind this combined modality approach is that in many cases breast cancer has microscopically disseminated outside of the range of the surgical knife at the time of diagnosis.[1] The microscopic involvement of the regional lymph nodes with tumor is currently considered the strongest indicator of this dissemination. It has been shown in reported studies that when there are positive nodes in mastectomy specimens the chance of recurrence is high. Since chemotherapy can kill tumor cells anywhere in the body and is effective against clinically evident metastatic breast cancer it has become the prime candidate to combine with locally eradicative therapy.

In 1972 the National Cancer Institute launched a large-scale controlled trial of the use of chemotherapy as an adjuvant to surgical operation in women in whom cancer had already spread. This study was carried out by the National Surgical Adjuvant Breast Project (NSABP), headed by Dr. Bernard Fisher. Half of the women were given

L-phenylalanine mustard (L-Pam®) after radical mastectomy and half were given a placebo.[2] Treatment failures occurred in 22 percent of 108 patients receiving placebo and in 9.3 percent of 103 women given L-phenylalanine mustard. This difference was only statistically significant for premenopausal women and continued follow-up has shown no meaningful difference for women who are postmenopausal.

In 1973 Bonadonna at the National Cancer Institute of Milan began a study identical to Fisher's except that the chemotherapy was a three-drug combination called CMF (cytoxan, methotrexate, 5-fluorouracil), which had been found to be superior to L-phenylalanine mustard in advanced disease studies. In only 5.3 percent of 207 women who received CMF was there recurrence of cancer, as opposed to 24 percent of 179 women in whom surgical operation alone was done.[3] At the time these findings were reported the patients in the study had been followed for an average of only 14 months, although some had been observed for 27 months. In a further analysis made in April of 1976 the overall follow-up period from radical mastectomy was 17 months with an overall recurrence rate of 29.6 percent in the group treated only with surgical operation, as compared with 12 percent in the CMF-treated group. In women with four or more nodes, it was 47.1 percent for the control group, versus 16.4 percent for the CMF-treated patients. When the patterns of relapse were looked at the total difference in the incidence of local-regional relapse between the two treatment groups was 11.7 percent (21/179) for the control group, versus 2.4 percent (5/207) for the CMF-treated group, indicating a very high degree of local-regional control with the chemotherapy.[4]

Bonadonna[3] indicated that the "results should be considered with caution, since, at present the effects of this therapy on survival and possible long-term side effects remain unknown." He indicated that while the results were "promising" the optimism should be tempered by the consideration that it is too early to tell whether CMF therapy is merely delaying recurrence or actually lengthening survival. Since breast cancer is a chronic disease which may reappear as many as 20 years after initial surgical operation there is some validity to the above statement. Still Fisher[5] has shown in his ten-year analysis of his earlier Thiotepa adjuvant study that the diminished recurrence rate, in premenopausal women in whom four or more positive nodes are found, observed with Thio-tepa led to a survival gain at both five and ten years which correlated with diminished recurrence and was statistically significant. This study indicates a high probability that when five- and ten-year survival data are available a meaningful survival impact will be seen but only time will tell.

Despite the caution expressed it does appear that for the first time in a major cancer killer, well controlled randomized trials in breast cancer have demonstrated the soundness of the rationale for using prolonged surgical adjuvant chemotherapy. This has far-reaching implications for therapy in tumors in general and in breast cancer in particular.

These data now tend to downgrade the importance of arguments over the relative merits of one surgical procedure versus another. The lesser operations have been advocated for cosmetic purposes only and purely surgical trials have been testing the null hypothesis that less radical surgical procedures are as good as, but no better than, more radical ones. At this time, all modalities which have been considered for local and regional control must be evaluated and reevaluated in the light of findings indicating the effectiveness of a systemic agent. In essence, as systemic therapy becomes more effective it may become more likely that lesser surgical procedures could be comparable. However, it is critical that the nodal status of all patients be known since this is the strongest indication we now have for the applicability of systemic treatment. This requires that axillary staging be carried out, even if the patient has a segmental or total mastectomy.

The critical question facing a practicing clinician is what should he do for his patients today. While ideally one would like to have definitive long-term analysis available, therapeutic decisions have to be made today based on preliminary data. For Holland[6] the issue is clear cut. He considers the Bonadonna study of "monumental importance" and recommends the use of adjuvant chemotherapy. He states that "the risks of carcinogenesis, fatal drug intoxication and other morbidity are certainly much less hazard than the certain death that inexorably follows clinically evident metastatic cancer." On the other hand Constanza in the same journal states that "it is much too soon to regard chemoprophylaxis in breast cancer as a proven method of treatment." For now, she believes, it should not be under-

taken by nonresearch physicians. Currently all clinical trials sponsored by the National Cancer Institute utilize chemotherapy in all patients after mastectomy in whom positive nodes are found. The current "controls" are L-phenylalanine mustard or CMF. Clearly more clinical research is needed to fully delineate the optimal drug combination and the sequence and duration of use. Ideally all patients should be entered into research protocols. With the current state of oncologic practice this cannot be a reality. Practicing clinicians must weigh the evidence available and make the best judgment they can for patients. Nothing in medicine is fixed and the state of the art is always changing.

As has been stated by Fisher[7] the labeling of a study as "prospective" or "randomized" or as a "clinical trial" does not necessarily ensure the worth of the data produced. Prospective and randomized clinical trials are aimed at comparing two or more methods of treatment in similar groups of patients. For comparison of results of different trials it is mandatory that an exact description of categories be made available. When the critical variables of patient selection, experimental design, treatment regimens and evaluation of response are examined in studies being carried out at present, a significant lack of comparability is observed among them all. Some of the variations are the result of differing viewpoints on treatment potentials of the various modalities involved and some are due to differing definitions of clinical variables. The ways that surgical procedures, chemotherapy, immunotherapy and radiotherapy can be combined in the treatment of breast cancer are so manifold that it will be impossible to test more than a small fraction of all the combinations and sequences. However, it is crucial that the data resulting from these and other studies be sufficiently comparable so that future studies can be rationally planned and patient resources used as efficiently as possible. Unless all investigators are able to agree upon definitions in the basic standards of design the vicissitudes of performance will lead to inconsistent results that will only continue the controversies about the optimal therapy of breast cancer.

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CASE REPORTS

Refer to: Birnbaum L, Olsen JA: Customized reconstruction of the breast after radical and modified radical mastectomies. West J Med 125:388-390, Nov 1976

Customized Reconstruction of the Breast After Radical and Modified Radical Mastectomies

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IN LARGE NUMBERS of women the world over, radical and modified radical mastectomies have been carried out for the treatment of carcinoma of the breast. Breast reconstruction has been done in relatively few of these cases. Undoubtedly many of these women, because of age or good psychological adjustment, do not seek such reconstruction or see the need for it. Many women, however, desire such a procedure but have been asked to delay having it done until "cure" is assured. Others have been told that their deformities are of such a nature that it would be difficult or impossible to reconstruct the breast. Still others have been put off by the extensive and numerous surgical procedures that have been used in the past. Moreover, even plastic surgeons involved with attempts at reconstruction are often negative in their attitudes due to the inadequacy of the expected results with existing procedures.[1-4] Nevertheless, disfigurement caused by radical or modified mastectomy often produces profound emotional, sexual and marital problems in many if not most women, and if simple procedures were available for reconstruction many women would be led to have this procedure carried out.[5,6]

The procedure to be described is devised to allow customized breast reconstruction after either a radical or modified radical mastectomy in selected patients to produce results heretofore unobtainable with other procedures. Its execution is simple, although it requires several stages to complete. It has the advantage, however, that for each stage a minimal time in hospital is necessary, or none at all if done in an outpatient facility. It has the further advantage of allowing for reconstruction with results that approach normalcy in many patients in whom reconstruction in the past would have been deemed impossible.

The following case illustrates this type of customized reconstruction.

Report of a Case

A 49-year-old white woman, seven years after right radical mastectomy was carried out, sought consultation regarding reconstruction of her breast. She earlier had consulted two other plastic surgeons who had left her with the impression that reconstruction was not possible. She had a typical deformity consisting of an anterior chest wall defect consistent with pectoralis muscle removal with resultant subclavicular and axillary defects (see Figure 1).

An outline was made of the defect and a large inflatable silicone implant was specifically constructed for the patient with a sac in the region of the desired anterior projection (see Figure 2). The patient was then taken to surgery and through an existing scar the entire area of the defect was undermined and the implant was inserted. The wound was closed after the implant was filled with

Figure 1.—Preoperative view of patient seven years after right radical mastectomy.

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a sufficient amount of saline to place the skin under slight tension without compromising the circulation. Two months later the wound was reopened and an additional amount of saline was added to further stretch the skin.

Two months later a permanent two compartment gel-filled prosthesis was substituted for the inflatable one (see Figure 2). At the same time the patient's left breast was modified to match the reconstructed right breast and the nipple-areola complex was reconstructed by borrowing 50 percent of the areola from the normal side. Also in the same procedure a hand-carved silicone sponge implant was placed in the subclavicular and axillary defects to produce the desired correction (see Figure 3).

Discussion

Breast reconstruction in the past utilizing silicone prostheses has generally failed to customize the reconstruction to the patient's defect. Most often following the reconstruction there has been a mound produced on the chest that failed to match the existing breast or fill in where the pectoralis muscles were removed. This has led to a negative attitude by both patients and physicians as to the quality of reconstruction. With the described procedure, candidates for reconstruction should be anyone requesting it with the physical criteria for reconstruction and whose prognosis is reasonably good following a curative resection. If postoperative radiation has been used, there should be little evidence of radiation damage to the skin present. The general physical and mental health should be good and the patient should be aware of the risks and limitations of the procedure. Reconstruction can begin within a few days of the initial surgical operation, or if not then it should be done approximately six months later so that there will be maturation and softening of the scars.

The procedure described should in no way mask any skin recurrences of the carcinoma. Should there be recurrences, they can be dealt with in whatever manner is deemed appropriate by the general surgeon caring for the patient. Obviously this may entail undoing the reconstructive result, but since the reconstructive procedures

Figure 2.—Custom-made silicone prosthetic implant for patient seen in Figure 1. On the left is the inflatable initial implant, on the right is a two-compartment permanent gel-filled implant.

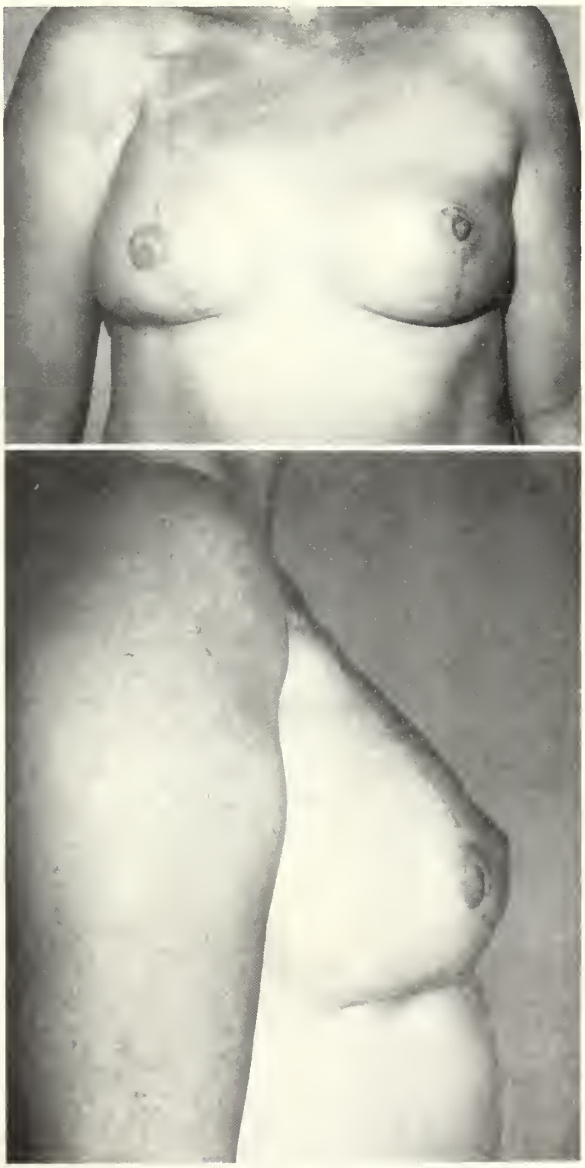

Figure 3.—Status of the patient three months postoperatively.

can be classified as minor surgical procedures, little would be lost. Should some patients succumb to their disease, most of these would have lived their remaining days as "whole" women.

Reconstruction would be aided if the initial surgical operation were done through a transverse incision and if an attempt were made, were it appropriate, to save the nipple-areola complex by transplanting it as a graft to a site on the abdomen. Ths latter procedure should only be done after biopsy of the dermis under the nipple shows it to be tumor free. It could then be used in the reconstruction after the expanding procedures have been accomplished.[7]

Summary

Procedures are advocated for breast reconstruction in patients in whom radical and modified radical mastectomy has been done. This reconstruction includes the restoration of the nipple-areola complex as well as existing muscular defects. The approach has led to gratifying results in some patients for whom in the past reconstruction might have been deemed impossible with the more conventional techniques available.

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Angina Pectoris in Mitral Stenosis — Observations on a Mechanism

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A VARIETY of different chest pains, including angina pectoris, have been described in patients with mitral stenosis.[1,2] Several series have indicated a 5 to 15 percent incidence of typical effort angina pectoris in patients with mitral stenosis.[3-5] A wide range of explanations has been offered for this phenomenon and consensus does not exist; some consider the relationship only coincidental.[6] This report describes the case of a patient with severe mitral stenosis and pulmonary hypertension with effort angina. Findings on evaluation showed normal coronary arteries and pronounced hypotension with exercise. These data support the previously proposed mechanism of inadequate cardiac output with exercise resulting in inadequate coronary perfusion as a cause of angina pectoris in patients with mitral stenosis.

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Report of a Case

In a 43-year-old man there were murmurs consistent with valvular rheumatic heart disease known since 1960. The patient remained asymptomatic until July 1973 when atrial fibrillation and pulmonary edema developed. The rhythm reverted spontaneously to normal sinus rhythm, and the patient's clinical condition improved following diuresis. Subsequently, cardiac catheterization was carried out. The catheterization findings were consistent with calcific mitral stenosis with mild aortic insufficiency (see Table 1). Since only mild effort dyspnea was present at this point and commissurotomy was not felt to be feasible, it was elected to begin a regimen of digoxin and quinidine. In the ensuing months the effort dyspnea slowly increased. Also, the patient noted a substernal constriction or pressure which he clearly distinguished from dyspnea. This occurred in addition to dyspnea with more pronounced exertion and was relieved with five to ten minutes of rest.

In December 1974 the patient was admitted to hospital at Naval Regional Medical Center, Oakland, with subacute pulmonary edema. His condition improved notably with diuresis. Findings on physical examination after diuresis included blood pressure, 110/68 mm of mercury; pulse, 80 beats and regular; mean jugular venous pressure, 5 cm vertically above the sternal angle, carotid pulses normal, and chest clear to auscultation. On cardiac examination there were a right ventricular lift parasternally, increased first heart

TABLE 1.—*Cardiac Catheterization Data*

	Study of August 1973		*Study of January 1975 (before surgical operation)*	
Right atrial pressure	A wave (A) 16 mm Hg	mean 10	A 19 mm Hg	mean 12
	V wave (V) 12 mm Hg		V 12 mm Hg	
Pulmonary artery pressure	60/35 mm Hg	mean 45	110/33 mm Hg	mean 70
Pulmonary wedge pressure	A 28 mm Hg	mean 26	A 35 mm Hg	mean 32
	V 32 mm Hg		V 35 mm Hg	
Left ventricular pressure	100/10 mm Hg		118/6 mm Hg	
Aortic pressure	100/69 mm Hg		118/65 mm Hg	
Mean mitral gradient	16 mm Hg		25 mm Hg	
Cardiac index	1.84 L/min/m^2		1.89 L/min/m^2	
Mitral valve area	.8 cm^2		.7 cm^2	

Aortic insufficiency and mitral insufficiency were assessed as mild by angiography on both occasions.

sound (S_1), narrowly split second heart sound with pulmonic component increased, 2/6 apical diastolic rumble extending through to S_1 with presystolic accentuation. A 2/6 short decrescendo blowing diastolic murmur was present at the left sternal border and a 1/6 blowing holosystolic murmur at the apex. No hepatomegaly or edema was present.

Since the patient again felt relatively well and questioned the necessity of surgical operation, a treadmill test was carried out for functional evaluation. The patient completed three minutes of Stage I (1.7 mph, 10 percent grade) and 20 seconds of Stage II (2.5 mph, 12 percent grade) using the Bruce protocol.[7] He stopped because of dyspnea and substernal constriction. He noted no lightheadedness or alteration in consciousness and recovered to baseline within ten minutes. Blood pressure and heart rate are recorded in Table 2. Cardiac catheterization was repeated one week later (see Table 1). Findings on coronary angiography were completely normal.

Uncomplicated mitral valve replacement was carried out with a 29 Bjork Shiley prosthetic device one week after catheterization. Aortic insufficiency was assessed as mild at operation and the aortic valve left untouched. The postoperative course was uneventful, with pronounced improvement in effort tolerance and no further substernal pain with effort. Clinical evaluation three months postoperatively showed a normally functioning prosthetic valve with signs of reduced pulmonary hypertension. The aortic insufficiency murmur was barely audible. On repeat treadmill testing, the patient completed two and a half minutes of Stage III (3.4 mph, 14 percent grade) of the Bruce protocol before stopping because of leg fatigue primarily and also dyspnea. There was no angina, hypotension or ST-T abnormalities (see Table 2 and Figure 1).

TABLE 2.—*Treadmill Data*

	Blood Pressure in mm Hg	*Heart Rate Beats/Min.*
Before Surgical Operation		
Resting	120/80	73
Stage I, 2 min.	110/70	140
3 min.	50/35	142
After exercise, 1 min.	50/35	120
2 min.	100/60	112
After Surgical Operation		
Resting	120/80	69
Stage I, 3 min.	150/80	114
Stage II, 3 min.	160/80	129
Stage III, 2½ min.	180/85	156
After exercise, 1 min.	150/80	126

Discussion

The effort-related substernal constriction in this patient before surgical operation was typical of angina pectoris. Pronounced ST segment depression was recorded during the initial stress electrocardiogram but since he was receiving digoxin and quinidine, since the resting electrocardiogram was abnormal and since severe right ventricular hypertrophy was present, these repolarization changes are not necessarily reflective of myocardial ischemia. The lack of ST segment abnormalities on exercise testing postoperatively, despite continuation of digoxin and quinidine administration, does indicate an ischemic cause for the preoperative abnormalities. The clinical history, however, left no doubt that the patient was experiencing the symptom complex of angina pectoris.

Chest pain with mitral stenosis is relatively common and has been described in a number of reports since 1891.[8] Some of these descriptions have been of nonanginal pain, such as the hypercyanotic angina reported by Burgess and Ellis[1] and the prolonged chest pains described by Viar and Harrison.[2] Other reports have dealt with

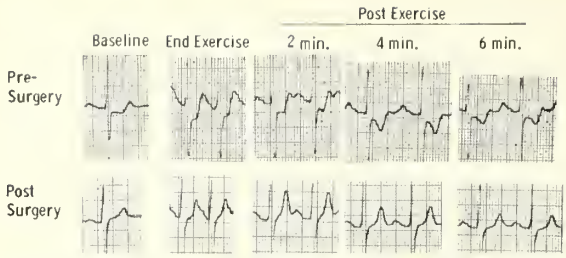

Figure 1.—Electrocardiographic complexes from Bruce Treadmill tests, V5. Patient was receiving digoxin and quinidine, in the same dose, during both exercise tests.

typical angina pectoris. Several studies in the British literature indicate a 5 to 15 percent incidence of typical angina pectoris in mitral stenosis.[3-5] These authors note the association of angina with severe mitral stenosis, severe pulmonary hypertension, or both. They attribute the angina to inadequate coronary blood flow due to inability to increase cardiac output with exercise. Stuckey further observed that a low fixed cardiac output with inadequate exercise increase is the common factor in other structural cardiac defects associated with angina, such as aortic stenosis, pulmonic stenosis or pulmonary hypertension. These data were collected before the general use of many current diagnostic techniques. Coronary atherosclerosis had to be excluded on presumptive clinical grounds (predominantly young female patients) or autopsy findings when available. Hemodynamic data with exercise were generally not available.

More recent studies have described sophisticated hemodynamic evaluation of exercise in mitral stenosis but do not include patients with angina. Bruce and co-workers reported hypotension with exercise in patients with mitral stenosis.[9] Frank and associates noted that coronary blood flow was dependent on central arterial pressure in these patients.[10] In those with mitral stenosis in whom hypotension developed with exercise there was a concomitant decrease in coronary blood flow. In cardiology texts there is no consensus on this question at present. Friedberg states "considering the frequent occurrence of mitral stenosis and angina pectoris as separate entities, the comparatively rare coexistence of the two conditions in the same patient must be explained as accidental, not causal."[6] Hurst concludes "the relevance of data supporting many of the conclusions seems to be open to question. In general, typical angina of effort in mitral stenosis should lead one to look for associated aortic valvular disease or coronary atherosclerosis."[11]

Other reports have suggested rheumatic coronary arteritis,[12] coronary artery emboli,[13] dilatation of the pulmonary artery[2] and compression of the left coronary artery between left atrium and pulmonary artery[14] as causes of angina in these patients. The data from this patient support the theory of Wood[5] and Stuckey.[3] With severe pulmonary hypertension and severe mitral stenosis, there were two obstructive lesions in series in the patient. The profound hypotension that occurred with exercise probably represents an extreme example of inability to maintain adequate cardiac output, commensurate with the increased demands of exercise. Coronary hypoperfusion almost certainly existed when angina developed since the arterial blood pressure was 50/35 mm of mercury. The data would suggest that the ischemic pain was generated in the severely hypertrophied right ventricle rather than the relatively normal and underfilled left ventricle. While the resting left ventricular pressure exceeded that of the right ventricle, this relationship was very likely reversed with exercise as systemic and left ventricular pressure fell. In any case the data indicate inadequate supply as a major abnormality in this patient's imbalanced myocardial oxygen supply and demand with exercise.

A single case will not finally resolve these questions. This case does support the most plausible explanation for this phenomenon. The currently available diagnostic techniques should allow definite resolution of this long standing controversy.

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Medicine and the Quality of Life

QUALITY OF LIFE increasingly is being identified as a goal of medicine and health care. In the July issue, the editors began a forum for discussing the actual and ideal relationships between medicine and the quality of life by printing seven articles expressing differing views. The following comments were generated by those articles and ones in succeeding issues.

Readers are invited to take part in a continuation of this forum by submitting their comments, written as succinctly as possible. As many of these as space permits will be published in future issues. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement to summarize the dialogue that has taken place.

A Clinical Challenge

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HEARTIEST CONGRATULATIONS on this quality of life forum.

We urge the WESTERN JOURNAL to use every journalistic device possible to keep it going. It would be well to broaden it to include others, especially those persons with chronic illnesses, members of the health industry and those in professional careers who "process" great numbers of ill persons and their multitude of bureaucratic forms. Clearly this need is a consequence of an increasingly general concern as manifest in the responses. Something seems amiss, and there is a general dissatisfaction that the quality of life of ill persons has not been improved (improved usually means prolonged rather than cured—that in itself may be part of the disillusionment). The dissatisfaction exists in spite of unbelievable gains in biomedical science, vast improvements in health technology and great social accommodations to support these gains (for example, brain definition of death and the recently implemented Social Security support for end-stage uremia). Trying to understand the nature of this dissatisfaction is a growing challenge to everyone—not just to physicians.

We feel that at the heart of the forum (now that Public Health has conquered infection) is an increasingly anguishing question: What is the nature of illness (understanding that it is more than pathophysiology)? Dependent on our answer to this primary question, then, will be our understanding of and attitude toward equally agonizing questions: what is the nature of health care (realizing that it is more than technical intervention); and what is to be the role of the physician?

In this forum during the last several months, a number of articles have come forth that have significant implications in regard to these questions. On our part, we have been immersed in a number of studies of chronic illnesses which also have significant implications. However, the implications of the forum articles and of our studies point in quite different directions. In each case it is from this quality-of-life question that the divergencies stem. The implication in many of the articles in the forum is that quality of life is an ideal or can be a given—a product that a physician because of his special role and training can, and therefore somehow *should*, bestow on a patient. Note, for instance, Elam's[1] proposal in the July issue that medicine "fails to fulfill the expectations of a number of consumer groups." In the same issue Sobel[2] points out that the physician, because of his own "narcissism" is loath to dispel this illusion. In fact, how many physicians, when a patient appears before them wishing to be relieved of illnesses and suffering, are able truthfully to share with the patient what he and the physician can really do and not do, and what would be required of the patient? Often the patient is a passive recipient and both patient and physician resort to the illusion of a "technical cure." It is this illusion of cure that appears to us to be the central clinical problem in the quality of life dissatisfaction. And it is the passive-recipient state of the patient that contributes to it. In our present health care system, the patient is in fact not only passive but mendicant, and we have done much in our profession and our system to make him so. He expects that he can be given this magical product, this longed-for quality of life.

Our experience in studying chronic illnesses over time has convinced us otherwise—not only that the quality of life cannot be given, but that it cannot in fact be maintained without a patient's own active participation. It is just this continuing participation, with the personal dignity and sovereignty it entails, that is the measure of his quality of life.[3]

These conclusions were reached from a series of studies (which will continue for two more years before publication of results) that were begun in the late 1960's. A group of clinicians of various disciplines working on the biomedical frontier in the experimental protocols of end-stage uremia had become concerned with the excessive price in happiness and personal integration that patients had to pay in order to have their lives prolonged by renal dialysis and kidney transplantation. We began to follow the cases of a number of patients from onset of illness to rehabilitation or death, monitoring relationships between the psychological and social variables and those pathophysiological and technical ones relating to the progress of the disease. From these observations, several systemmatic studies evolved.

Our first study (a ten-year follow-up) consisted of 20 patients. We chose ten who had died that year and asked the computer to match these with ten who were still living. The matching was done using eight variables, all in the surgical, medical and immunological areas. The study was then retrospective in terms of the former lives and the clinical careers of those ten who had died, and prospective for those who lived (four continue after eight years). The independent variable in this study was

a human one, consisting of psychological and social factors. The psychological factors included character, the characteristic and repetitive behavioral reactions to the stresses of the treatment regimen, personal integrity and the ability to participate in the program. Social data revolved around demographic factors present in early childhood. The indications from this study relative to the maintenance of the quality of life are that those persons who are at the highest risk for death and complications are those who respond to recurring life stresses with demoralization, depression and helplessness. Most often these same persons were those who were "deprived" during early developmental periods. Conversely those who fare the best are those who are able to understand the medical regimen and its complications and can form and continue an active clinical partnership with a constant physician.

As a consequence of this continuous monitoring we developed close relationships with these patients and their families. We were forced to acknowledge the constant presence of a number of latent clinical truths:

- Until the scientific problems are solved, chronic illnesses are incurable.
- Since they are incurable, they need to be managed by long-term treatment programs.
- To be successful, these management programs require the continuous collaboration of the patient in a clinical partnership with a constant physician. The patient must be able to understand the nature of the disease, to monitor changes, report alterations—indeed, figuratively to become his own physician.
- Since these management programs are very expensive and require expensive technologies, they are often beyond the ability of the family to pay and require the commitment of tremendous social resources.
- These social resources are processed by a complicated health delivery system which grows as a powerful political structure and tends to alienate both the physician and the patient. The patient is reduced to mendicancy and the freedom and responsibility of the physician is limited because the options within this health delivery system are socially determined.

With all of these pressures on an ill person, the core of his experience becomes one of helplessness. The essential question then becomes: "In the face of this helplessness, how does a person maintain his quality of life?" The answer we found, in broad generalities, was that this maintenance centers around the constant ability of the patient to continue to affirm himself, to collaborate in his care through learning, to endure certain pathological and technical givens, and actively to negotiate and bargain for his needs.

Our second study arose naturally from the first and was an attempt to continue to study the quality of life following kidney transplantation. The systematic protocol was temporarily funded by the National Institutes of Mental Health and continually supported by the Kaiser Family Foundation. This study was designed to include three phases, of which the first, a Benchmark Survey, recently has been completed. For this survey we received 1,100 names from the active files of nine transplant centers, located in three large metropolitan areas. A questionnaire consisting of 800 variables was answered to interviewers by 627 patients in their own homes (40 percent of the 1,100 could not be located). Partial conclusions relevant to this forum are as follows: 90 percent reported significant side effects associated with the graft, of which 30 percent were felt to be significantly disturbing to family and work relationships. Of the 627 patients, 50 percent are unemployed and receive support from public agencies. By 36 percent it was felt to be difficult to obtain enough money to make ends meet. Predominant in the answers to the interviews was the tendency for the patients to idealize their condition, with a large percentage of those whose condition was poor and who felt unhappy expressing the expectation that things would improve in the next five years—this is in direct opposition to scientific fact.

We participated in a third study conducted by other agencies and confined to the area of renal dialysis. It was concerned largely with the technical procedures involved, surveying more than 5,000 participants in 91 facilities. Its objective was to assure quality control through a standardization of procedures. The assumption here (virtually taken for granted) was that quality control (of the scientific and technical variables) would affect the outcome and thereby improve a patient's quality of life. In the study three primary outcome variables (morbidity, mortality, cause of death) were correlated against a series of clinical risk factors (race, sex, age, original diagnosis, complications). The protocol (processed by the Rand Corporation using the complicated and sophisticated Delphi technique) shows that there is no correlation between technical intervention and outcome of mortality and morbidity. The risk in these categories is the same as in the general population of people having these risk factors. While some feel that the risk factors are not clearly delineated, we are convinced that nothing the end-stage uremia program does in a technical or scientific way changes the well known outcome of these risk factors. For example, if one has diabetes mellitus, the risk is very high for morbidity and mortality. What alters that risk is whether or not one is a "good" patient and has a good relationship with a physician or clinical team who works with you constantly.

The implications of these studies are clear: the outcome of the treatment is related not so much to the technology or its application as to who the patient is as a person and what his relationship is to a caring physician.

Findings in our other studies reinforce these conclusions (clinical observations from other chronic illness forms are confirming. We have included infectious bowel disease, sickle cell anemia, diabetes mellitus and the postgastrectomy dumping syndrome). Technical measures for the patient, without considering his personal attributes and his relationship to the physician, will not assure quality of life. It is not what is given to him in the treatment, but what he can contribute to it, the extent to which he can and will participate in the process, that is the determinate measure. By this scale, then, the goal of therapy undergoes a significant change. The objective now becomes to increase a patient's dignity, his sovereignty and his ability to contribute actively to the partnership.

These conclusions place us at the opposite pole from those who idealize or feel that quality of life can be given. If our findings are relevant, they bring into question the whole present concept of health care, posing a challenge to the increasing reliance on technology and requiring a reappraisal of the word "care."

All of these considerations arise from the same source, the quality of life question. It is clear from the contributions already received in your series and the divergence of views that has resulted, that the issue is a seminal one for the medical profession and society as a whole. Its resolution will determine not only the future direction of the health care system, but the role (and the freedom) of physicians themselves. It is an issue that calls for the deepest appraisal and concern by all members of society, in truth a social commitment. It is for this reason that we urge the WESTERN JOURNAL to continue the forum and do everything you can to broaden it to include the widest possible participation.

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Five Levels of Interaction

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THERE ARE at least five levels on which medicine interacts broadly with people and their institutions to improve the quality of life.

1. Medicine may relieve suffering and correct reversible illness that prevents individual expression and limits individual opportunity. This is the most obvious and tangible benefit of medicine, and it was the day-to-day appreciation of this that got me through my internship.

2. Medicine through high standards of public health may improve the function of a society and the vitality of its institutions. This benefit is an historical achievement in developed societies. This effect may be greater than the sum of the individual health benefits in society.

3. Biomedical research contributes importantly to our capacity for self-determination by completing and extending our concept of reality. This allows us to act on the basis of knowledge and to recognize our domains of ignorance. Imperfect as it is and will be, it avoids the reliance on superstition.

4. Medicine provides the framework for understanding the effect of environmental factors on health, in order to redesign our communities toward healthful living. Biomedical research provides us with tools by which to audit our performance.

5. Medicine is an anthropologically important ritual of social expression that commits us to an active role in coming to grips with the human condition. It is also a stark drama which defines this condition by the allegory of disease, patient and physician.

The first point is the traditional ideal of the physician and is far better discussed by the Oath of Hippocrates than I could do here. The second point is an integral part of the current debate on medical services in developing societies, in particular the apparent exception of overpopulation. It is a fascinating topic, very poorly studied until now, with early data suggesting a more complex role for the level of medical services than was expected.[1] The breadth of the topic precludes discussion in this forum, however.

The third point is under much dispute. Ivan Illich would have us believe that medicine has become a threat to individual liberty and one's control over one's own life.[2] I see the converse: that medicine has created more opportunities for humanity to exert self-determination by removing some disability and death. It is undeniable, however, that medicine has created disability by postponing or preventing some death, but that is an option that did not exist before biomedical science, and one that society has accepted. Other aspects of this point have been discussed recently in this journal.[3]

The last two points are somewhat exotic. They are seldom addressed directly, and since they are unlikely to be discussed elsewhere in this forum I think that they deserve our attention here.

Within the last eight years, popular concern over environmental quality found political expression in the ecology movement. Without pretending that our situation today is ideal, it is clear that we have made substantial progress. Despite the problems that remain, pollution standards are stricter and better enforced, population growth in the United States has altered so that demographic stability is possible in the next generation and cities throughout the nation (even Baltimore) are slowing or halting their slides into decay. Unfortunately, medicine as a professional constituency has made very little impact on this profoundly health-related process, except for the few who participate in pollutant standards review. Despite an eloquent call for medical involvement in a new enterprise of environmental health,[4] few physicians have recognized the opportunities for participation in environmental health planning.[5] Medicine as a whole has ignored the fundamental opportunities that exist for improving community health through planning. (One physician who saw them, however, was Anton Chekhov, whose interest in environmental health is expressed by his character Dr. Astrov in *Uncle Vanya* and who was personally involved in such matters in the Ukraine.)

Community planning, which has gone far beyond the bounds of city planning and zoning, is a powerful and frequently subtle social tool with a large capacity for benefit and for abuse. Done well, it can be a force for advancement in the quality of life. Done poorly or insensitively, it can be a threat to life and to individual liberty. In a society as complex as ours planning is unavoidable. To abdicate from medical participation in the process is to allow it to run blindly in matters of health.

The last point is perhaps the most diffuse and difficult to discuss. One must now perceive medicine in a very different context. Medicine is a practical art, a theoretical system and also a means of communication. As a house officer, I respond to a cardiac arrest and carry out cardiopulmonary resuscitation: I am working at a practical task, but I am also expressing in deed an antifatalist, future-oriented world view. The medical point of view, phenomenological and inductive, is both a product of this culture and a powerful shaping force within it, just as other concepts of medicine are in other cultures.[6]

It is worth remembering the physician protagonist of Camus' *The Plague*. Dr. Rieux performed his duties in the microcosm of the city of Oran without seeking to avoid the plague. He did not make a conscious decision to remain, although he thought about the implications of his action; the decision was already made when he became a physician. He recognized his pathetically inadequate power to halt the epidemic. But he did what he could and in so doing demonstrated his humanity to the representative of mankind, the journalist Rambert. Rambert then made the difficult decision not to define his existence as a negative being (by fleeing Oran and accepting the love of another person), but instead to declare his humanity affirmatively by action. Likewise, medicine is a drama of assertion, the ritual of confirming our capacity to change that which threatens us and potentially to understand that which we cannot change. We may err and we may be weak in many cases, but we act and when it is necessary or wiser, given present knowledge, to refrain from acting we are discontent.

Surely this role of medicine enhances the quality of life.

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Refer to: Guidotti TL: Five levels of interaction, *In* Medicine and the quality of life—A forum. West J Med 125:395, Nov 1976

Continuing Education and Continuing Quality of Life

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WHILE THE initial contributors to the forum raised important points with regard to the relationship between medicine and the quality of American life, they did not look at this in relation to the enormous explosion of knowledge and technology that has taken place in the past 30 years. One of the roles of continuing medical education is to make this new knowledge and technology available to practicing physicians, and to try to evaluate its effect on the physicians' competence and on patient care. While the effects of new knowledge and technology on patient care have been widely discussed, the equally profound effect of that knowledge and technology on the physicians' role has been largely ignored. At the very least, it has led to an increasing dependence of physicians on technical skills—with the result that failure is now equated with malpractice. Also the technical components of the physicians' role can now be broken down into segments that can be done equally well by other professions. Secondary and tertiary care physicians have become increasingly dependent on technical skills, with all the associated vulnerability that accompanies this. The competency of technical skills can also be monitored and measured by nonphysicians. Computer monitoring of diagnosis and care is only one aspect of this trend.

This knowledge explosion has also led to increased medical specialization—with serious problems of fragmentation, organization and communication. It has taken medicine to a stage where the major diseases remaining are those produced by ourselves and our technology. New techniques enable us to palliate more and more chronic diseases in order to maintain our increasingly unhealthy environment and lifestyles. The costs of such palliatives are already prohibitive; as costs continue to increase, national health insurance and more intense utilization review become inevitable. Unfortunately they carry no guarantee of any improvement in the quality of life.

Medical specialization with its associated fragmentation has made continuity of care impossible—if a health professional is expected to provide the continuity. It is this situation which generates an insistent demand for new physician and patient roles and relationships.

True continuity of care can be maintained only by patients themselves. Patients, however, are not encouraged to take an active responsibility for either their own treatment or their own health. The most important role change for patients must enable them to provide their own continuity of care. A major new role for primary care physicians must be to provide education and support for that change.

It is extremely important that physicians realize that the freedom of both physicians and patients is inextricably linked. The old style of patient dependency has become a trap. As patients who are neither accustomed or encouraged to take responsibility for their own health realize that the old patient role no longer works, they will seek some form of redress. If patients do not move toward more independence, they will transfer more and more responsibility to government. In turn this will mean that physicians and other providers will become increasingly dependent on government.

Increasing governmental intervention is the conventional response to the potentials and problems that accompany new technology. The resulting bureaucracy tends to become not accountable; it is also least able to make the kind of continuing and flexible changes that the rapid growth in medical knowledge and technology will require.

If physicians thus expect to retain their own independence, they must begin to foster independent patients. This is a major new role—and it entails a new role for continuing medical education. Continuing medical education must provide physicians with the ability to change their own role while providing them with the communication and human management skills to educate their patients to independence.

Traditional medical education is inappropriate for this new role and, like the bureaucracy, cannot change rapidly enough to be responsive to new knowledge. United States naval history offers an analogy to this. In the period from 1860 to 1900 the American navy experienced a technological revolution similar in speed and magnitude to that which has occurred in medicine during the past 30 years. Naval leaders, trying to cope with the new rifled gunnery, steel hulls and steam propulsion, attempted to contain all the new potential within the familiar pattern of the British ship of the line. Steam ships were built with sails, simply because it was inconceivable that they could be built any other way. At a time when the effective range of a six-inch gun was three miles, the navy spent most of its time training sailors to repel boarders with pikes and small arms. This is the situation in medical education today.

New knowledge and technology made to fit into old familiar patterns has led to the present "crisis" in medical care. Patients are the unutilized resource that the medical system desperately needs. Patients are the basic and most constant link connecting doctor to doctor. The communication and coordinating potential of this link has hardly been explored. The major role of a primary care physician must be to foster the independence of his patients, to enable the patient to be able to provide his own continuity of care and to accept responsibility for his health. The concept of a "consumer" with its overtones of taking and being overfed must be replaced with the new role of a person who is able to use wisely the freedom of making decisions to keep himself healthy and to share the responsibility for decisions made to restore health when he is sick.

Such change will not be easy. It does, however, have the potential of organizing a technologically sophisticated health system with minimal use of bureaucracy. As it increases both the freedom and responsibility of physician and patient roles, it stands to improve the quality of life for both. To adopt and accept these new roles, the physician needs new skills; most of all he will need the ability to change. The new role of continuing medical education is to provide the physician with the knowledge and skills to participate actively in change.

Refer to: Allan D, Bruegel R: Continuing education and continuing quality of life, *In* Medicine and the quality of life —A forum. West J Med 125:396, Nov 1976

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

TENS in the Treatment of Heroin Dependency

To the Editor: I would like to make a few comments regarding the use of acupuncture in heroin dependency. Since 1973 I have used this treatment at the San Francisco Drug Treatment Program, Inc., first having used manual stimulation and progressing through "staplepuncture." I agree with Dr. Tennant's article in the Western Journal [Tennant FS Jr: Outpatient heroin detoxification with acupuncture and staplepuncture. West J Med 125:191-194, Sep 1976] in which he states that the duration of relief lasts 30 minutes to 18 hours. (An occasional person has received relief for 36 hours.) However, I have stopped using staplepuncture for the following reasons: Although relief did occur, it was not sufficiently prolonged; second, persons who had attended the clinic regularly for counseling became erratic in attendance; third, some did not return to have the staples removed; fourth, the staff was getting requests for more frequent treatments, more than we could handle without hiring new personnel.

Therefore, I searched for a method whereby heroin dependent persons could provide relief for themselves, and I have started using transcutaneous electric nerve stimulation (TENS) of the auricular branch of the vagus nerve. TENS has been compared with acupuncture in the treatment of low back pain;[1] the results were found to be comparable. Dr. Tennant neglected to point out that staplepuncture was done in the general area supplied by the auricular branch of the vagus nerve. With the use of a modified stethoscope, potassium chloride cotton electrodes are placed onto the concha of the ear and connected to the TENS generator. The patient turns up the ampli-

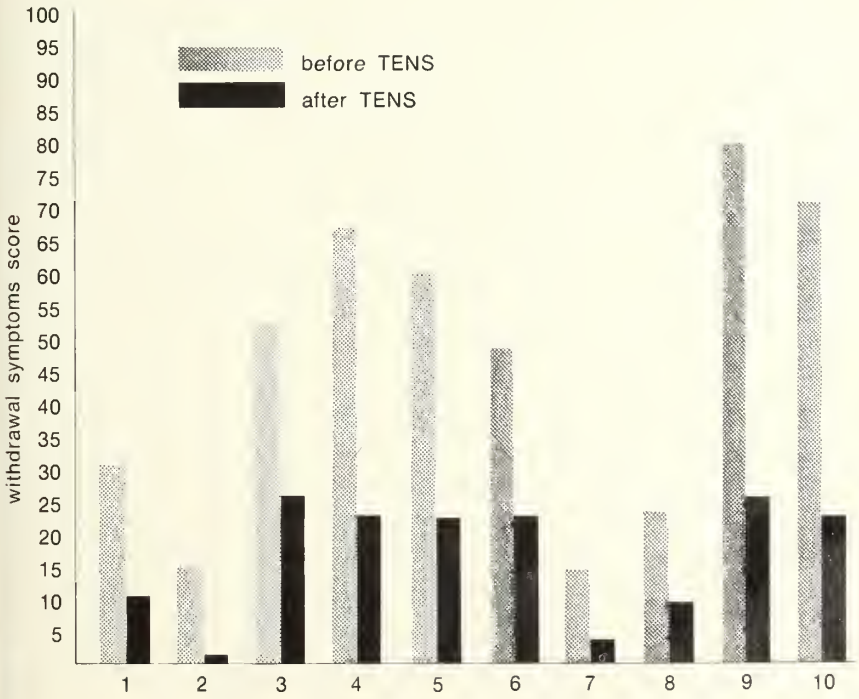

Figure 1.—Comparison of withdrawal symptom score in ten patients who received transcutaneous electric nerve stimulation (TENS) of the auricular branch of the vagus nerve.

tude until he receives adequate but nonpainful stimulation (approximately 10 to 15 milliamps, frequency at 50 to 75 pulses per second).

The graph shown in Figure 1 gives findings in the first ten patients treated. These patients (whose average length of addiction was 7.7 years) received a total of 21 treatments. In those who received more than one treatment the scores were averaged. Each treatment lasted 15 to 30 minutes. (The score is based on the following measures: withdrawal, namely lacrimation, rhinorrhea, myalgia, arthralgia, nausea and abdominal cramps, sweating, chills and general malaise.) The preliminary results indicate TENS works as well as acupuncture. Eventually, it is hoped that TENS generators will be given to heroin dependent persons for home use. As Dr. Tennant states "If our subjects had been inpatients and acupuncture and electrical stimulation had been administered more than once per day, detoxification would undoubtedly have been achieved . . . ."

In the years that I have been working with drug dependency, I have found the use of acupuncture an acceptable adjunct to medications for relief of withdrawal symptoms.

MANUEL L. KARELL, MD
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More on Preventive Medicine

TO THE EDITOR: As an academician who occasionally cannot resist the urge to "chant the litany of practicing preventive medicine," I feel compelled to respond to a letter from Gordon Breitman, MD, in the September 1976 issue. (Breitman G: Preventive medicine—A myth? West J Med 125:236, Sep 1976). Dr. Breitman correctly identifies cigarette smoking as "one of the most publicized causes of morbidity and mortality in the country." He concludes that "smoking continues to increase steadily. The government's effort was a failure." The first of these conclusions is wrong. The second is valid only if one applies an extremely demanding standard of effectiveness, such as the virtual elimination of cigarette smoking.

A recent major survey found that the percentage of adult males who report that they smoke cigarettes dropped from 53 percent in 1964 to 39 percent in 1975. The post-World War II upward trend in smoking by women, which continued for several years following issuance of the Surgeon General's report (1964), may have been reversed in the present decade: currently, 29 percent of women report that they smoke, compared with 30.5 percent in 1970.[1]

If Dr. Breitman is not convinced by the survey's findings, subject as they are to self-reporting bias, I would urge him to examine objective data on cigarette production and sales. These data show that, on a per capita basis, cigarette smoking leveled off in 1974 and actually declined slightly in 1975.[2] This is particularly impressive when one realizes that certain conditions were conducive to significant increases in smoking during these years. For example, beginning in 1974 relative real cigarette prices were falling for the first time in a decade. It has been demonstrated repeatedly that cigarette consumption is responsive to this economic factor.[3]

The same objective production and sales data indicate that the peak rate of smoking, achieved the year prior to the Surgeon General's report, has never been equaled since. Furthermore, in the years following the report, average "tar" and nicotine per cigarette have decreased 28 and 18 percent respectively (and more than 50 percent each since the smoking-health warnings in the early 1950's).[4] Thus the intake of these presumably toxic substances has dropped considerably.

While such data suggest to me that the antismoking publicity has had a significant impact, they do not provide a reasonable indication of the magnitude of the impact. The true measure of the effectiveness of the campaign is not how much smoking there is today compared with how much there was several years ago. Rather, it is a comparison of today's smoking behavior with how much smoking *would have been expected today had the antismoking campaign never materialized.* For a variety of reasons—including the rapid growth in smoking by women, decreases in per cigarette nicotine dosage, and so on—it seems highly unlikely that a half century's steady upward trend in per capita cigarette consumption would have ceased suddenly and "naturally" the year of the Surgeon General's report. To the contrary, the logical expectation would have been for continued increases. My own research suggests that per capita cigarette consumption would have been a fifth to a third greater than it is today had

the publicity and legislation of the past decade never occurred.[5] To my way of thinking such a record hardly constitutes a failure.

I have no doubts that the clinician's job of counseling patients on health behavior can be extremely frustrating. Perhaps only a minority of such patients alter their deleterious habits, and of these perhaps only a minority maintain their new life-styles over the years. But Dr. Breitman and like-minded colleagues can console themselves with the realization that there are significant numbers of successes (possibly more readily visible in aggregate data than within a single medical practice), and that these individuals may be the beneficiaries of the most important and effective health care advice available, be it from government publicity or their private physicians or a combination of these and other sources.

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Arbitration Agreements

To the Editor: Butler's article on arbitration was very interesting [Butler JR Jr: Arbitration agreements and your malpractice coverage (Informed Opinion). West J Med 125:253-258, Sep 1976]. I especially appreciated his comments on the California Medical Association's arbitration form being overcautious as to specifying that signing the agreement is not a precondition to receiving medical care. In my own office portion of my practice I tend to decline to accept nonemergency cases where the patient is a new patient and reluctant to sign. I have been willing to initial out the phrase in the booklet that explains that signing is not a precondition to being taken care of when it is my assessment that the patient would not be harmed by traveling a few miles to see another pediatrician.

The discussion of a performance bond of about $500 was also interesting and informative. In agreements where arbitration is negotiated in advance and where patients have been used to signing such agreements in the various offices that they go to, I think it would not be much of a problem to get patients to sign agreements that have this as a feature. I think the percentage of people who are reluctant to sign is a little higher than what is generally reported in the literature. Teachers and attorneys, and their families, seem to be quite reluctant to sign in general, although I have had a generous sprinkling of both groups go ahead and sign. For the time being I do not intend to take a chance of running into more resistance to sign by adding the performance bond. The principle outlined by Butler does seem quite sound but he is not a physician. As a physician who has been using arbitration for some time I suspect that the rate of people balking at signing would go up quite a bit with that feature added to the agreements.

There is an area of reluctance to sign that has not been mentioned in the literature to my knowledge. In my experience County Welfare Departments and Juvenile Court judges have, to date, shown great reluctance to cooperate in signing arbitration agreements on behalf of foster children. Foster parents are willing to sign but their signatures probably would not hold up because they are rarely the legal guardian. I predict that this will continue to be an area of resistance but fortunately such cases make up only a relatively small percentage of anyone's total practice. Should others have found judges who are willing to sign such agreements on behalf of foster children I would be quite interested to hear from them.

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Merced-Mariposa Medical Society
Merced, California

* * *

To the Editor: This letter is in response to the article in the September issue of the Western Journal entitled "Arbitration and Malpractice Coverage," by James Butler. There are two points in this informative article that I would like to discuss. They concern the manner in which the California Medical Association is proceeding with its arbitration project and refer to the manner in which arbitration agreements are approached with our patients. Mr. Butler in his article contends that we are employing an overcautious approach requesting patients to sign an arbitration agreement. It would seem to me that under the

provisions of AB 1xx, the manner in which the CMA is approaching this problem at the present time is the proper one. Any attempts at coercing patients to sign, as I understand it, would invalidate the arbitration agreement. I think this point should be clarified.

The other point deals with employing a rather substantial bond as a deterrent to having an arbitration proceeding filed. Perhaps it is not generally known that the CMA has established an "arbitration fund" to be used by patients who do not have enough funds to implement such a proceeding. The purpose of this is to mitigate the oft used cry that the contingency fee is the poor man's key to the courthouse. By advocating an increased bond we are actually placing an impediment to the arbitration proceeding that is, in my opinion, unnecessary. If arbitration is to be successful, the impediments artificially created to detour patients from utilizing this method of solving differences would be totally unsatisfactory and criticism of them would be absolutely justifiable.

I feel these points should be clarified in order to insure that physicians will not obtain an erroneous approach to the arbitration proceedings which is advocated in this otherwise generally good overview of the arbitration process. I must again emphasize that this is a partnership that we are employing with our patients and I feel that any attempt to coerce and impose unusually artificial and high barriers to disagreements would tend to make this entire process less effective.

NICHOLAS P. KRIKES, MD
San Bernardino, CA

* * *

TO THE EDITOR: It is with great interest that I read the article in the September 1976 issue of the WESTERN JOURNAL by James R. Butler, Jr., entitled "Arbitration Agreements and Your Malpractice Coverage" [West J Med 125:253-258, Sep 1976].

I would agree with most of what Mr. Butler has to say regarding arbitration, both in its present form and what it portends for the future.

However, I feel that there is a serious error in the last paragraph on page 257, extending to the top of page 258. Mr. Butler, in discussing the California Medical Association-California Hospital Association arbitration agreement, states "The agreement expressly provides that a patient's signature on the form is not a precondition to furnishing of medical services. There is no necessity for this overcautious approach . . . " I believe that the Supreme Court of the State of California in its decision in *Tunkl v. Regents of University of California,* 60 Cal. 2nd 92, 383 P. 2d 441, 32 Cal. Rptr. 33 (1963) has given us a very convincing reason for such an "overcautious approach."

After noting that health care providers offer a public service, which means that their contracts affect the public interest, the Court *struck down* an exculpatory agreement offered by a hospital to its patients on a take-it-or-leave-it basis. The Court observed that "The admission room of a hospital contains no bargaining table, where, as in a private business transaction, the parties can debate the terms of their contract." If a significant number of physicians offer arbitration contracts on a take-it-or-leave-it basis, it is quite possible that the California Supreme Court will echo the *Tunkl* decision and hold that a doctor's waiting room—like a hospital's admission room—contains no bargaining table, and strike down patient-physician arbitration agreements or severely circumscribe their use. California has no cases yet on the books upholding the basic legal validity of patient-physician arbitration contracts. Thus, there must be a test case, and if that test case arises out of facts in which it appears that the physician "coerced" his patients into signing the arbitration agreement, then the California Supreme Court may rule unfavorably—not just toward arbitration on a take-it-or-leave-it basis, but toward *all* patient-physician arbitration agreements. Physicians should remember, therefore, that the rulings of the Appellate Court constitute the law of the state and affect all the physicians equally.

If arbitration is truly "an idea whose time has come," we of the medical profession must be very cautious and circumspect in its application until the questionable and untested areas are fully worked out.

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Refer to: Bergeson PS, Lipow HW: Improving community based pediatric residencies by local affiliation—The Phoenix experiencee (Medical Education). West J Med 125:401-406, Nov 1976

Improving Community Based Pediatric Residencies by Local Affiliation

The Phoenix Experience

PAUL S. BERGESON, MD, *Phoenix,* and HERMAN W. LIPOW, MD, *San Francisco*

Community hospital graduate medical education programs have been judged deficient in several areas when compared with university programs. Generally community programs are smaller, they have a greater percentage of foreign house officers and unfilled house staff positions, and their graduates do less well on specialty board examinations. Difficulties may exist in offering a balanced and broad-based educational exposure. Four separate pediatric residencies in Phoenix became affiliated in 1972. The traditional deficiencies have been overcome, and a very popular and well-balanced program has ensued. Additionally, wasteful duplication has been avoided. Disadvantages have included complex scheduling and loss of continual close contact with house officers. Assigning patients to residents for continuity of care has been difficult. Experiences gained in this amalgamation may well apply to other hospitals facing similar problems. Local consortiums, such as this, fit well into university affiliated programs or statewide organizations.

POSTGRADUATE TRAINING PROGRAMS in hospitals not affiliated with a university are under close scrutiny by the Residency Review Committee of the American Medical Association, and many medical educators feel that the multifaceted demands of specialty training necessitate university affiliation. Those at unaffiliated hospitals argue that their trainees have been well educated and are as qualified for the realities of medical practice as physicians trained in university centers.

Community residency programs without affiliation with universities have been compared with university affiliated programs, and several traditionally deficient areas have been shown to exist. Nonaffiliated programs, on an average, tend to be smaller and their graduates do less well on the specialty board examinations.[1] A higher number of house staff positions in these hospitals is filled by foreign graduates and the overall percentage of positions filled is less;[2,3] there are differences

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ABBREVIATIONS USED IN TEXT
FMG = foreign medical graduates
PHAPP = Phoenix Hospitals Affiliated Pediatric Program

in teaching methods and philosophy of education;[4] there has been difficulty in providing adequate faculty and a broad educational experience.[5] These observations deserve careful consideration in planning postgraduate training programs.

Community hospital programs are under pressure to improve teaching and quality but are limited by budget restrictions. The cost of their teaching programs has been supported by patient charges in private hospitals (usually community sponsored, nonprofit organizations) and by local tax assessment for city and county hospitals. The increasing concern of consumer groups and industry over the rising cost of medical care has made any proposal to increase the amount of money spent on training programs untenable.

Our pediatric community decided to amalgamate five hospitals into one city-wide pediatric residency program—the Phoenix Hospitals Affiliated Pediatric Program (PHAPP). The program directors feel that all the individual training programs have been strengthened significantly by this arrangement and that the affiliation has overcome some problems inherent in community based programs and has received an enthusiastic reception by current and prospective trainees.

This is a report of the experience during a one-year planning period and the first two and a half years of operation.

Phoenix, a rapidly growing city with a metropolitan population of about 1¼ million people, serves as the medical referral center for central and northern Arizona. Before the amalgamation in 1972, Phoenix had three fully approved pediatric residency programs: Good Samaritan and St. Joseph's hospitals (private, nonprofit community hospitals), and the Maricopa County (tax-supported) General Hospital. The services provided by these hospitals are listed in Table 1. A fourth hospital (the Phoenix Indian Medical Center) had lost its approval because it did not have all the services necessary to maintain approval. The three approved hospitals rotated their residents through the Arizona Children's Hospital (a surgically-oriented children's hospital sponsored and funded by the Arizona Crippled Children's Services).

TABLE 1.—*Services Provided by Hospitals in PHAPP Consortium in 1972*

Hospitals	*Number of Beds*			*Deliveries Per Year*
	Total	*Pediatric*	*Neonatal*	
St. Joseph's	550	45	40	3,100
Good Samaritan	699	40	40	3,000
Maricopa County	500	52	40	3,500
Phoenix Indian	190	41	10	600
Arizona Children's	84	84	17	..
	2,023	262	147	10,200

PHAPP = Phoenix Hospitals Affiliated Pediatric Program.

In 1972 the three pediatric residency programs were well established. The Good Samaritan and St. Joseph's hospitals had developed subspecialty programs based on the interests of the program directors and full-time hospital-based faculty; Good Samaritan Hospital had a large cystic fibrosis and pediatric cardiology service, whereas St. Joseph's Hospital was recognized for its pediatric nephrology and hematology-oncology capability. Maricopa and Phoenix Indian hospitals offered an overwhelmingly active outpatient service with a large caseload of acutely ill children suffering primarily from infectious diseases and trauma.

Before amalgamation the individual strengths of the respective programs were recognized by the directors, and limited subspecialty exchange rotation to other hospitals was in effect. In 1968 the pediatric programs had combined some of their teaching activities—such as weekly grand rounds and a joint lecture-seminar series—to provide a sizable audience for the speakers and diminish the need for local consultants to repeat presentations on the same subject.

At the time pediatric residency programs were established in Phoenix (1954-1964), the state had no medical school. The University of Arizona medical school in Tucson (125 miles away) was established in 1967, and since 1969 has provided a pediatric monthly guest professor to Phoenix. Medical students from Tucson could choose from several electives in the Phoenix hospitals, but interchange at the resident level was almost nil.

The Amalgamation

In early 1972 planning for a merger was started. Little information was available about previous mergers,[5,6] although several programs had undergone affiliation.[7-9] The difficulties to be faced were not apparent at the start. No overall master plan could be created since the problems

and their solutions had to be established by the process of continuing dialogue. A timetable of one year was set.

The most crucial problem was recruitment of house staff. Despite the Maricopa County Hospital's excellent program and caseload, foreign-trained residents occupied most of the house staff positions, so that one of the goals of the proposed affiliation was to attract a higher proportion of house staff trained in the United States. The possibility was considered of having the two private hospitals serve as base hospitals for recruiting for the entire program. After much deliberation this plan was rejected as discriminatory, one that might create first- and second-class hospitals. Once it was agreed that the three major hospitals must be equal in all respects, progress in reaching accord in other areas proceeded rapidly (the Phoenix Indian Medical Center obtained residents through its own United States Public Health Service program).

The details of providing for payment of salaries, uniforms, professional liability insurance, hospitalization insurance and food in the combined program became a challenge. Initially we planned that each component hospital would pay salaries and administrative costs to a central organization which, in turn, would contract for all the required services. It soon became apparent that the logistics and the politics of working with five hospital administrations (including one each at the county, state and federal level) were almost insurmountable. Long-established hospital rivalries and fear of the loss of autonomy may have accounted for some of the difficulties, even though these were never specifically expressed.

The compromise solution was to amalgamate the individual programs into one, with central recruiting under one National Intern and Resident Matching Program number, with each resident assigned to a "base hospital" for pay and fringe benefit purposes. This gave each hospital administrator control of a specific number of residents, even though the residents might spend only four to six months of the training year at that base hospital.

Rather than undertake the expense of a separate office and secretary, the decision was made to use one of the already existing pediatric education offices and to rotate the office and workload every two years. The initial placement was in the Maricopa County Hospital, bypassing the problem of choosing between the two private hospitals. The Director of Pediatric Education of the hospital which housed the PHAPP was automatically the titular head of the program. The successful functioning of the affiliation, however, hinged on the weekly meeting of all program directors and full-time faculty where the significant decisions were made. This meeting was held immediately after the weekly grand rounds, when the physicians involved were already congregated at the host hospital.

Results

Advantages

The amalgamation changed many areas which had been identified as problems in the community programs: size, foreign house staff, increased percentage of vacant house staff positions and lower board examination scores. The affiliation program resulted in a faculty with 18 full-time and 2 half-time members, 35 house staff positions, and more than 10,000 pediatric admissions per year.

Foreign medical graduates (FMG) made up 19 percent of the house staff in 1974-1975 and 5 percent in 1975-1976 (Table 2); the average in the United States was 32 percent for university and 59 percent for unaffiliated programs.[3] All but one of the pediatric level-1 staff were American graduates. The FMG generally had outstanding credentials and experience and were equal to the United States graduates in overall performance. All the positions were filled easily in 1975-1976.

Since the merger the scores on the written examination of the American Board of Pediatrics have increased remarkably. Table 3 lists the average scores of the graduates since 1972 when the examination scores were first standardized. We feel the improvement resulted from improved education as well as the recruitment of house officers with better educational qualifications.

Whereas the largest full-time faculty of any single hospital before the merger was 5, the house staff now has exposure to all 20 faculty members, representing 11 different pediatric subspecialties. This is an unusual depth for a nonuniversity program.

The cost of medical education to the individual hospitals is mostly in salaries to house officers and the faculty members based there.[10] The number of house officer positions is related to service requirements. The faculty members are hired by the individual hospitals for purposes of education

and patient care; their commitments vary widely between education and service, depending on the unique needs of the hospital and the faculty member's arrangement with his own hospital. Salary costs are not available because these are usually confidential; however, no increase in costs could be attributed to the amalgamation because no new staff members were hired.

To date, one of the most attractive aspects of the program has been the broadened range of patients seen, including several ethnic groups and all income ranges. Also the house staff has an opportunity to observe disease states that are common in poverty level Indian and Mexican-American populations, as well as the disease spectrum of the middle class. Notably absent is a skewed experience, heavily weighted in a limited number of subspecialties. The professional reputation of several members of the teaching staff attracts large numbers of patients with problems in their subspecialties, so that overall the total program balances well with the multiple fields of interest represented. Most of the residents have been lavish in their praise of the advantages of this multiple hospital rotation and the broader training experience.

Perhaps the most significant advantage of amalgamation is that no single hospital has to provide all the training opportunities necessary for a quality program. Each hospital has been able to concentrate on developing its individual strengths and to rely on the others to round out the educational experience of the trainees. Wasteful duplication of services has been avoided and outstanding subspecialty services have been developed. The program now recruits additional faculty because of community and program needs, and not because of individual hospital expansion programs.

No attempt is made to have all residents rotate equally through each service in every hospital. Such an arrangement would create unacceptably short rotations. It is recognized that several services are similar in educational opportunity, such as the inpatient service at the two private hospitals.

An attempt is made to plan each individual rotation so it provides a balance of services, including private and public hospitals, general and subspecialty ambulatory clinics, and general and specialty hospital practice. Rotations are five and a half to six weeks in duration. Elective rotations provide an opportunity for a resident to obtain further training in any areas that he feels his schedule has not included.

Additional electives in pediatric neurology, radiology and infectious disease have been made possible, and no rotations have been eliminated. Additional outreach activities include participation in a learning disabilities school and a city-wide child abuse program.

Disadvantages

The major difficulty encountered so far is in providing an opportunity for the house staff to follow individual patients over the three-year training period. Rotations have become so complex that such arrangements for follow-up and continuity of patient care have been achieved only recently. Selected patients are assigned to a team of a junior and senior resident who together see a cohort of long-term patients one day a week. A resident will follow this group of patients throughout his training. A new junior resident is assigned to the team each July as the previous junior house officer achieves senior resident status.

Ambulatory training is carried out in separate outpatient facilities in each hospital. One private hospital has a prepaid clinic, while the other has a charity clinic. Both the County and Indian Hospitals have large ambulatory services. Faculty in the outpatient facilities include a full-time specialist in ambulatory pediatrics, as well as attending pediatricians from the private practice community. A community pediatric rotation provides widespread exposure to several health care organizations in the city.

TABLE 2.—*Foreign-Trained Pediatric House Staff in Phoenix (1969-1975)*

	Percent
1969-70	63
1970-71	52
1971-72	44
1972-73	52
Recruitment through combined program	
1973-74	36
1974-75	19
1974-75 (PL-1)	0
1975-76	5

PL-1 = pediatric level-1 staff.

TABLE 3.—*Average Scores on Written Examination of the American Board of Pediatrics*

Before amalgamation		*After amalgamation*	
1971	280	1973	466
1972	378	1974	433
		1975	508

A second problem which our program shares with other training programs is the difficulty of providing graded responsibility during the second and third years of pediatric training. Because there is an increasing demand for three years of general pediatric training, the program directors have devoted considerable time to developing a large variety of electives, bringing in guest lecturers, offering research opportunities and providing increased patient responsibility in this third year.

A third problem has been increasing difficulty in identifying the specific training deficits and personal problems of individual residents. In a small program the deficiencies of individual residents quickly become known to the teaching staff, and corrective measures can be taken almost informally. With a large number of residents rotating through many services with many attending physicians, the problems and deficiencies of a resident are harder to delineate and the loss of continual contact with one teacher makes corrective intervention more difficult. Monthly written evaluations of the performance of each resident by his attending physician were already being made and, after some deliberation, a faculty group discussion was added to evaluate the performance and progress of each resident periodically. Once a resident with a problem is identified, a remedial plan is made and the resident is observed during his next rotation.

Schedules, too, have become extremely complex. Since trainees are rotated among five hospitals, a house staff manual has been compiled to describe the idiosyncrasies of the different hospitals and services. A uniform approach to vacations, electives, hours of duty and other issues has been worked out.

Another new experience has been the increased complexity of the candidate selection process. Lengthy working discussions were necessary before reaching final agreement on the ranking of candidates for the program.

In view of the many difficulties listed, and many not mentioned, it is doubtful that the new program could have been organized in less than a year. The program merger has been accomplished with remarkably little display of physician egotism or hospital territoriality. Our task was made easier because no hospital demanded a dominant role. This avoided the creation of a caste system, which has occurred in other city-wide affiliations.

Discussion and Conclusions

There are many advantages inherent in community hospital medical education programs. The PHAPP directors, as well as others,[11,12] have been impressed with the changing attitudes of current medical school graduates. Many candidates are less interested or are openly cynical about the expenditures of energy and money in pursuing rare diseases, research and superspecialization. Community programs, with their emphasis on training competent practitioners, fulfill the needs of trainees with such an outlook. Beeson[13] has commented on the beneficial effect on society of this philosophy in training. Toomey[14] encourages both community hospitals and university centers to make their own unique contributions to physician education.

PHAPP represents a cooperative effort that is much like that envisioned by Stross and associates,[15] who proposed a statewide postgraduate organization as a means of handling such problems as quality control of teaching programs, encouragement of community response to local physician manpower needs and regulation of the use of foreign medical school graduates. Such a system would centralize the responsibility of many programs, encourage their financing at a state or federal level, standardize the program content and evaluate procedures, and respond to the needs of the individual states. The Phoenix program represents an attempt to accomplish many of those tasks locally and therefore might fit well into a larger statewide scheme.

The Association of American Medical Colleges has recommended that university medical centers assume the responsibility for graduate medical education.[16,17] The PHAPP directors feel that there is room to question the wisdom of that recommendation. If medical schools are given that responsibility, they should take full advantage of the experiences, talents and abilities of those local physicians who have struggled to develop excellent programs in community hospitals. Some strengths and resources of the local community may not be immediately apparent. Gains in teaching experience through an affiliation with local hospitals should be encouraged and could result in a great mutual strengthening of programs.

From our experience we believe many problems in graduate education can be solved locally; indeed, decisions on how to achieve change should be made locally. This does not preclude a larger

institution, such as a university or a statewide program, from sponsoring or coordinating that program. As Stross has suggested, local institutions should be represented in a spirit of cooperation rather than imposition by mandate.

It seems unwarranted to perpetuate separate training programs with limited or unbalanced resources in geographic proximity if the goal of postgraduate training is to produce a graduate with broad exposure to pathology and varied expertise. The experience of PHAPP in combining programs has resulted in broader experience and greater depth of training, and has more than compensated for the problems encountered in the merger.

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Approaches to Leg Cramps

All sorts of therapies have been devised for leg cramps . . . I have an interesting gimmick that I use and I pass it along to you . . . I find that most leg cramps occur, whether in men or women, . . . when the leg is stretched. Therefore, if a pillow is put at the bottom of the bed, when the patient rolls over at night and begins to extend the leg, the foot hits the pillow. The patient feels it and it doesn't necessarily wake from sleep, but tends to retract (flex) the leg. The thigh is perhaps flexed, too. In any case, it prevents the full extension that might occur in the sleeping state.

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Surgical Services in a Navajo Indian Hospital

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UNTIL A YEAR AGO, the word Navajo to me meant only a marauding Indian in the old days of the Southwest. Looking around for something interesting to do for a year or so, I heard from AMDOC (a nonprofit service directing health professionals into areas of need)[1] that there was an opening for a surgeon in the Public Health Service Indian Hospital at Shiprock, New Mexico. There had been no surgeon in this 75-bed hospital for six months. I decided to give it a try.

The Navajo Reservation is larger than the state of West Virginia. The greater portion is in Arizona, but the southern part of Utah and a northwestern section of New Mexico are included. For the most part it is high desert (5,000 feet) cut by deep arroyos and dotted with fantastic volcanic rock formations and low mountains. About 150,000 Navajos occupy this area of the great southwest plateau. They have been here since about 1500 A.D., after conquering the agrarian Pueblo people, part of whose culture they adopted. For the most part, however, the Navajos remain chiefly sheepherders and cattlemen. At present, a new irrigation project is being developed which, eventually, will put 110,000 acres under cultivation. Today, much of life on the reservation is very primitive. Only 26 percent of houses have running water and flush toilets, 25 percent have electricity, 75 percent have no refrigeration.[2] The pickup truck as the replacement of the horse and wagon is one of the few concessions to modern living. There is almost total unemployment except for government jobs, home industries such as silversmithing and weaving, and marginal farming. Boarding schools, funded federally or by various religious groups, and regular public day schools, funded by the state in the larger population centers, provide education where busing is a necessity of life.

Health care, which is completely "socialized" and entirely free, is dispensed through a system of clinics scattered about the reservation and by six more or less strategically located Public Health Hospitals at Crownpoint, Winslow, Gallup, Fort Defiance, Shiprock and Tuba City. The hospital at Gallup is the largest, has greater specialization and is the usual center of referral for the other hospitals. Neurosurgical and certain other cases must be sent to Albuquerque, 250 miles away, or to Phoenix, 300 miles distant. Patient transfer is by air. Each hospital is administered by a Public Health officer who is advised by a local Indian Health Board. Financing is provided by the Department of Health, Education, and Welfare. The staff usually includes several young general medical officers who are in the Public Health Service. In addition, there are varying numbers of specialists in medicine, surgery, pediatrics, radiology and obstetrics-gynecology. They may be in the "corps" or may work under civil service. Aside from most of the doctors, dentists, nurses and pharmacists, the hospital staff is Navajo. There are usually several medical students helping out.

There are very few Navajos trained in the

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health profession—a few registered nurses and only two physicians. One of these is Dr. Taylor McKenzie, who spends much of his time developing a much needed health education program with an American Indian School of Medicine the ultimate goal. The preclinical years would be based at Northern Arizona University at Flagstaff, Arizona, with the clinical years centered at a new facility in Shiprock, New Mexico. It is hoped that if funding can be obtained the first class would convene in September 1977.

Shiprock, named after an enormous volcanic rock formation just outside of town, is in the northeast corner of the reservation close to the four corners, where Utah, Colorado, Arizona and New Mexico meet. The hospital here serves about 40,000 Indians most of whom live on small farms in the desert. Near Shiprock is the huge four-corners power plant which strip mines the Navajo coal deposits. About 500 Navajos are employed here—the only large source of nongovernment money.

Generally speaking, the care provided in the hospital is very adequate. The patient load is rarely more than 60 to 75 percent occupancy. The large outpatient department, which handles about 83,000 visits yearly, is staffed by general medical officers except for specialist clinics. A pharmacy with five full-time pharmacists dispenses medicines at no cost to patients. There is one operating room which is shared by the surgeon and the obstetrics-gynecology department, a recovery room with two beds and a 30-bed medical-surgical ward. At present, we are fortunate to have two board-certified anesthesiologists in attendance, but in the past there has usually been one overworked nurse-anesthetist.

The operating room is well run. The scrub nurses are, for the most part, licensed professional nurses or technicians. The equipment is very good. With the help of one or two general medical officers, the surgeon is expected to do "general surgery" in the older meaning of the term. This is particularly applicable to orthopedics. I find myself pinning ankles and hips, reducing fractures and dusting off Campbell's and De Palma's textbooks for refresher courses.

One irritating difficulty in trying to schedule elective surgical procedures is the fact that we can never be sure that the patient will appear on the appointed day—or, if he does appear, that it will be at 7 p.m. on the evening before the operation instead of during the early afternoon. Rarely does the patient make the effort to notify the doctor or the hospital that he will be unable to keep his appointment. When queried as to why he did not appear, numerous excuses are made—no transportation, muddy roads or had to attend a funeral or shear sheep. One wonders if this complacent attitude on the part of a patient who has no financial interest in his medical treatment may be expected in any system of socialized medicine. In any case it makes efficient scheduling of surgical cases impossible. When I first encountered this type of behavior, it occurred to me that it might be due in part to the fact that I was new and unknown to the Indian patients, but this was only a small factor. The same disregard for keeping appointments is experienced by Dr. McKenzie, a Navajo surgeon who has been in the area for many years. Taking the doctor and the delivery of medical care for granted is characteristic of a large percentage of the Navajo population. The attitude that "you are paid by the government to take care of me, so do it" is commonplace. Therefore, the development of a rapport between doctor and patient similar to that experienced in private practice is often lacking.

Language barriers on the Navajo reservation can pose a real problem. Probably only a third of the Indians speak fluent English, a third understand some and speak less, and a third speak only Navajo. The speaking of English is discouraged in many homes. Until recently the speaking of Navajo was discouraged in the government boarding schools, but this policy is changing rapidly. Most of the teenagers and younger children have been exposed to English at school and understand it well but many of the older people living in the remote areas of the reservation rarely hear spoken English. Only a few have telephones or television.

The Navajo language is difficult to learn, and few of the doctors ever master more than a few key medical expressions. The language has been put in writing only in recent decades. Because of its complexity Navajos were widely used in World War II as "talkers" instead of using code. The inability to converse with patients is overcome by the use of interpreters and bilingual hospital employees. The resultant communication leaves much to be desired and is time-consuming. Complicated questions may be beyond the ability of the interpreter to convey to the patient, or vice versa. These language difficulties combined with the somber, shy nature of these people do not

TABLE 1.—*Inpatient Surgical Procedures, PHS Indian Hospital, Shiprock, New Mexico, January 1, 1975 to January 1, 1976*

Orthopedic procedures	55
Cholecystectomy	51
Appendectomy	40
Exploratory laparotomy	24
Skin graft	19
Skin and subcutaneous tissue	18
Ventral hernia	15
Inguinal hernia	13
Proctological	11
Colostomy	8
Thyroidectomy	7
Breast biopsy	7
Orchidopexy	7
Tendon repair	7
Bronchoscopy	7
Cystoscopy	6
Debridement	4
Thoracotomy	2

make for spirited rapport. When I complained to a Navajo friend that patients rarely said "how are you or thank you" he answered that they rarely use such terms with each other.

Further problems are created by long distances and life-styles made necessary in this very arid region of the United States. In order to have sufficient acreage for the flocks of sheep and cattle, the population must be scattered over wide areas. Roads are bad, and at times impassable even for the universal pickup truck. Outside of small towns or along the few highways there are no telephones, no electricity, no running water. Water must be carried by trucks from community wells, often over many miles. Conditions within the house or hogan are so primitive that patients who could ordinarily be discharged to recuperate at home must remain in the hospital for considerably longer periods. This is especially true in the case of children who would ordinarily be discharged the day after a hernia repair but must be kept in the hospital for lack of hygienic conditions at home. Moist compresses or change of bandages by the patient are difficult or impossible. The presence of medically unsophisticated people in the home makes observation of injuries risky. This results in numerous admissions for conditions which might otherwise be treated at home.

During the year of 1975 we discharged about 700 surgical patients. Of these, 75 percent were classed as emergency admissions. There were more than 100 patients involved in motor vehicle accidents. In half of these cases the accidents were related to alcohol ingestion. Alcoholism, six times the national average, is a major problem on the reservation.[3] Trauma resulting from the outdoor life style of the people, including horseback riding and sheepherding, accounted for many of the injuries. There were more than 100 fractures treated in this group. Second and third degree burns were present in 22 cases.

Other emergency admissions were not unlike those seen in other hospitals except that acute cholecystitis was more frequently seen. Many patients were admitted with abdominal pain which, in most cases, proved to be appendicitis. A somewhat unusual differential diagnosis was distinguishing appendicitis from enteritis due to Shigella infection—which is very common, especally during the dry season.

The types of elective surgical cases seen were not unique, with the exception of the chronic cholecystitis cases. Indians have a considerably higher incidence of gallstones,[4] which may be due to a lower lecithin and bile acid content of the bile.[5] We did more cholecystectomies than any other operation. Gallstone ileus, fistula, abscesses and biliary carcinoma[6] are common. This is the experience in all Indian hospitals. Surgical procedures for various types of hernias, hydroceles, thyroids, benign breast lesions and undescended testes, and a smattering of others including orthopedic procedures and an occasional thoracotomy, make up the bulk of the surgical services. Carcinoma of the colon is almost unknown here. Several patients with ulcerating carcinomas of the breast refused surgical treatment. We carried out 301 inpatient operations (Table 1). There were 720 outpatient surgical procedures.

The medicine men in our area are frequently called upon to treat patients on whom we eventually operate. A "sing" to prepare the patient for surgery or to promote a satisfactory convalescence is common. In spite of the outward acceptance of Christianity in one form or another, most of the Navajos embrace the supernatural powers of the medicine man, which are entirely divorced from Christian monotheism. In certain psychosomatic problems the medicine men are probably of value, but psychosurgery in which they work to remove gallstones and appendices by sucking or scratching the abdomen can cause serious delay in getting proper treatment to the patient. We have had one and possibly two cases in which an appendix ruptured in the interval between "sing" and surgery. A recurrent attack of cholecystitis was said to result from the fact that the medicine man was "only able to remove one

of the stones." Treatments or "sings" by the medicine men are condoned by hospital authorities and are carried on at the hospital bed just as a priest might administer the last rites. Usually the medicine man is a little more active than a priest. There is much vocalizing and rattle shaking—which seem not to bother patients in adjoining beds. It is an interesting sidelight that these medicine men are well paid for their treatments. In an area where the average annual per capita income is $750,[7] a $100 charge is not to be taken lightly.

In spite of the minor difficulties encountered in this more or less remote area, the work has been interesting, the contacts with the young medical officers stimulating and desert living generally pleasant. The Navajos need our help in their efforts to gain self-sufficiency and working with them has been a rewarding experience. For a surgeon or other doctor who feels he is in a rut or who wants to live at a slower pace, the Indian Health Service is worth his consideration. It is not necessary to travel to a foreign land to find areas of real medical need.

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Rarity of Mediastinal Parathyroids

When patients come to you who've had an operation for primary hyperparathyroidism, and the tumor or tumors have not been found . . . your first thought is "My God, it's down in the mediastinum and we've got to split that patient's sternum!" Let me assure you that 99 and 44/100 percent of the time . . . that tumor is still in the neck; it's not down in the mediastinum, and so don't go cracking that fellow's chest open just because it wasn't found in the neck. In a recent series . . . in 100 percent of 22 reoperations for parathyroid disease, the tumor *was* in the neck and had been overlooked in the first operation.

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Pulmonary Aspiration in Anesthesia

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MASSIVE PULMONARY ASPIRATION during anesthesia may be a serious and lethal event; it carries a mortality of 62 percent.[1] Most commonly gastric contents are aspirated, although blood, pus and dislodged teeth may pass into major bronchi. In addition, pulmonary aspiration may occur with disorders of esophageal and gastrointestinal motility, states of reduced consciousness, debilitating diseases and central nervous system disorders.

Pulmonary aspiration of gastric contents during induction of anesthesia has been known for more than a century.[2] It was in 1941 that Hall noted the frequency of pulmonary aspiration during anesthesia for cesarean section.[3] Then, in a classic paper in 1946, Mendelson noted a high incidence of pulmonary aspiration of acid gastric contents during anesthesia for obstetric surgical procedures.[4] Mendelson identified two different types of pulmonary aspiration. The first is the obstructive type with aspiration of particulate gastric contents. This is largely a mechanical phenomenon involving obstruction of the larger airways resulting in acute asphyxia. The second type of pulmonary aspiration he described is due to aspiration of acid liquid vomitus, and may at first resemble an asthma attack. More recently, Bartlett and Gorbach defined aspiration pneumonia as a clinical manifestation of one of three types of aspiration: toxic liquid aspiration (Mendelson), aspiration of bacterial pathogens and aspiration of inert substances (such as food particles).[5]

During anesthesia, pulmonary aspiration occurs most commonly during induction—with a silent regurgitation of the acid vomitus. It has also been noted during emergence from anesthesia but may occur at any time. It has been well established that the pH and the volume of the aspirate determine the extent of the pulmonary injury, although the pH is the major etiologic factor.[4,7] Originally Mendelson advocated the administration of warmed antacids to reduce gastric acidity. However, it was not until Taylor and Pryse-Davis recommended orally given antacids in 1966 that this measure attracted interest and gained some acceptance.[8] Roberts and Shirley, considering the lethal nature of massive aspiration, conclude that all obstetric patients should be assumed to have full stomachs and should be managed with orally given antacids.[9] Hutchinson and Newson indicate that there may be a place for administration of antacids before general anesthesia in all patients.[10]

The risk of maternal morbidity from aspiration has been well documented in a number of articles.[9,11,12] Morbidity from aspiration may occur with any type of surgical operation and a large percentage of surgical candidates are at risk, although pregnant patients are subject to many predisposing factors that may lead to aspiration of gastric contents.[13,14] In particular, the number of cesarean sections carried out seems to be increasing, with the concurrent increase in risk of pulmonary aspiration. Some studies state that 34 percent of anesthetic obstetric deaths are secondary to aspiration, and that anesthetic deaths may represent up to 15 percent of all maternal deaths.[14-16] Aspiration pneumonitis then would be the fourth largest cause of death after hemorrhage, toxemia and infection. The death rate due to anesthesia may be as high as one maternal aspiration death per year for each community of one million people.[9]

In common with many patients in whom emergency surgical operation is required, obstetric patients may well have eaten recently and have a full stomach. However, even with many hours between the last meal and delivery of the neonate, gastric volume in a obstetric patient may easily exceed 50 ml.[8] Gastric stasis and delayed gastric emptying in anesthetic obstetric patients may be due to a number of causes: anatomic displacement of the stomach, pain, labor itself, analgesics

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and anxiety. In a parturient patient, the intrauterine fetus also increases intra-abdominal pressure and commonly causes a hiatal hernia, both predisposing the mother toward regurgitation. In addition, pulmonary aspiration is enhanced by diminishing the gag and cough reflexes by giving analgesic medications. Any surgical patient could easily possess one or many of these predisposing factors and would be a candidate for pulmonary aspiration.

Pathophysiology

The pathogenesis of pulmonary aspiration involves inhalation of either liquid or solid gastric contents. The acidity is the major etiological factor, as aspirated gastric contents with a pH less than 2.5 may produce significant pathology.[4,7] The volume of aspirate necessary to produce injury varies from study to study; however, most authors agree that a volume in adult humans greater than about 25 ml is sufficient.[9,18] After aspiration there is rapid distribution of vomitus with damage to pulmonary epithelium and capillaries. Because of the anatomic position of the right main stem bronchus, the right lung is more frequently involved.[13] A frothy, serosanguinous transudate appears and bronchospasm may be noted. Decrease in alveolar ventilation occurs and the V/Q ratio is notably altered. Clinically this produces cyanosis with apnea, quickly followed by rapid shallow breathing and tachycardia. Pulmonary compliance falls, and wheezes and rhonchi are noted along with frothy sputum as the patient becomes hypoxemic. The arterial blood pressure subsequently falls.[19] As the initial regurgitation is often silent, the signs and symptoms may not be noted until the syndrome is fulminant, some hours after the initial insult. The first symptoms have been likened to an asthmatic attack by some, and many show characteristics of pulmonary edema.

At necropsy both the trachea and bronchi are notably congested with pink frothy transudate. The lungs are heavy and resemble liver with gross and microscopic hemorrhage together with areas of atelectasis and overinflation. Subpleural hemorrhage and transudate are often noted. Viewed microscopically, the alveolar capillaries show pronounced congestion with edema in the alveoli together with desquamation of the bronchial epithelium. Clumps of bacteria and particles of food may also be mixed with the alveolar transudate.

Diagnosis

Perhaps the most valuable concept in the diagnosis of pulmonary aspiration is a high index of suspicion. With the predisposing factors common in obstetric patients and present in many surgical patients, the possibility of pulmonary aspiration is frequently present. Regurgitation is commonly silent, and patients become acutely ill 2 to 12 hours after the event. Initially, vomitus may be noted and then treatment should begin at once. Vigorous aspiration of the trachea may be diagnostic, and simultaneous paper-strip determination of pH from fluid from the pulmonary tree and the stomach may aid in estimation of severity and prognosis of the aspiration.[20] As time progresses, cyanosis, tachycardia, tachypnea, hypotension, wheezes, rhonchi and rales develop. As the pulmonary transudate increases, plasma volume decreases and blood pressure continues to fall with a concommitant decrease in cardiac output. On an x-ray film of the chest, scattered soft irregular mottled densities, greater on the right, may be seen. Studies of arterial blood gases show hypoxemia in the face of high inspired oxygen with a variable arterial carbon dioxide tension. A combined respiratory and metabolic acidosis is common.[21]

The pulmonary aspiration syndrome caused by aspiration of acid gastric contents may be mistaken for congestive heart failure, asthma, pulmonary emboli, pulmonary edema, adult respiratory distress syndrome or amniotic fluid emboli. However, true pulmonary edema and failure in the right portion of the heart may follow the insult of pulmonary aspiration of gastric contents.

Prevention

Before discussing successful treatment of pulmonary aspiration, attention should be given to adequate prevention. Preoperative starvation is a standard element in all operating room policies, with a period of six hours for adults being routine. Oral administration of antacids to increase gastric content pH has been established as highly effective.[8] Giving 15 ml of either magnesium hydroxide antacid or aluminum hydroxide antacid every two hours is accepted therapy; one dose of aniseed flavored 0.3 molar solution sodium citrate has been shown to be effective as a one-time dose in emergency situations.[22] Ideally, nasogastric intubation may be carried out and the upper gastrointestinal tract emptied before surgical operation

in patients at risk, although emptying may not be complete. Some have advocated induced vomiting; however, this is often ineffectual and unpleasant, and is rarely practiced. Postoperatively, use of nasogastric tubes may be associated with an increased incidence of pulmonary aspiration due to diminished cough and gag reflexes.

There are a number of maneuvers that anesthesiologists may employ to prevent or minimize aspiration. The use of local or conduction anesthesia, or awake intubation, would appear to decrease the incidence, although it does not guarantee that pulmonary aspiration will not occur.

Induction and intubation with a patient in a head-down position enables drainage of secretions and vomitus by gravity as well as patency of the airway. Some have advocated placement of the patient on the right side for intubation. Atropine may be given intravenously before induction for its vagus inhibiting effects, in addition to decreasing secretions. Intravenous administration of a small dose of d-tubocurarine hydrochloride diminishes the rise in intragastric pressure which may be caused by succinylcholine chloride given during induction. Preoxygenation for at least two minutes helps to denitrogenate the lungs and provides a valuable oxygen reserve. Cricoid pressure is effective and should be used.[23] Finally, a smooth rapid induction of anesthesia minimizes the risk of aspiration by depressing the vomiting center, and is followed by quick inactivation of the muscle component of vomiting with administration of a muscle relaxant. A cuffed endotracheal tube, rapidly inflated, should be used in almost every instance to help prevent pulmonary aspiration.

Management of Pulmonary Aspiration

A recent excellent review by McCormick outlines therapy currently in use for this condition. Mechanical maneuvers in treating pulmonary aspiration begin with immediate placement of the patient right side down and head down at an angle of about 20 to 25 degrees. The airway is laryngoscoped and cleared with rapid suction followed by oxygenation and intubation. Vigorous suction with intermittent oxygenation should follow, although bronchoscopy may be necessary to remove large food particles. As noted above, determination of the pH of the pulmonary aspirate, together with the pH of gastric contents, may provide valuable information. Lavage worsens pulmonary injury by further spreading the offending liquid and adding to the injury; it is ineffectual in neutralizing the aspirate and its use is contraindicated.

Use of oxygen is the hallmark of therapy, and spontaneous respiration is frequently inadequate to maintain acceptable arterial oxygen tensions with large aspirations. Mechanical ventilation is usually necessary for one to seven days as the cellular epithelium population regenerates and fluid balance and pulmonary dynamics are restored. Positive end expiratory pressure (PEEP) may be necessary in the face of persistent low arterial oxygen tension.

Medications employed include sodium bicarbonate to combat acidosis, which may be respiratory or metabolic in type, or both. Hypovolemia after massive pulmonary aspiration is common, secondary to loss of blood volume into the lungs. Replacement should be carried out with plasma or plasma substitutes while continually monitoring central venous pressure. Antispasmodics such as aminophyllin are used to combat bronchospasm. Administration of antibiotics as a prophylactic measure is controversial although it is mandatory when secondary injection occurs or when pathogenic organisms are aspirated. Steroid therapy is possibly beneficial during the first 72 hours. If the patient fails to recover totally after serious cerebral hypoxia, measures to decrease cerebral pressure should be begun, including hyperventilation, diuresis and adequate steroid therapy.

Conclusions

Pulmonary aspiration is a serious and possibly lethal event, often occurring during the course of general anesthesia. It produces a syndrome that may rapidly progress from subtle respiratory distress to respiratory failure, pulmonary edema and circulatory collapse. Prevention is the key to control of pulmonary aspiration, and a number of maneuvers are available and frequently helpful. They include strict dietary control, nasogastric intubation and oral administration of antacids. During the induction of general anesthesia, intravenously given atropine and d-tubocurarine hydrochloride, preoxygenation and cricoid pressure are extremely valuable techniques which may be used. In addition, the use of rapid, smooth induction followed by cuffed endotracheal tube intubation will decrease the risk of pulmonary aspiration.

Should aspiration occur, the airway must be immediately cleared and secured, and oxygen given to the patient continually. Tracheal suction

may be followed by intravenous administration of antibronchospasmatics and steroids. The hypoxemia and acidosis that follow require close arterial monitoring with mechanical ventilation. Finally, intravascular volume and pH need to be followed continuously and brought toward normal levels if necessary.

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Episiotomy Repair Techniques

It is very important in the repair of the episiotomy that a certain technique be followed so as not to incur either dyspareunia or even a painful episiotomy. I don't particularly care how you repair the vagina, whether it is by interrupted sutures or continuous suture, but I believe the suture should stop on the inside of the hymenal ring. No suture should be put through the hymen and no suture should be put over the hymen, such as a continuous whip stitch. Stop your vaginal closure on the inside of the hymen and then perhaps you could put one interrupted suture just beyond the hymen and then go on to do your perineal repair. One significant thing in the perineal repair, although it takes a little time and a little concentration, will reward you a great deal because of the lack of discomfort that occurs. When you are approximating the muscles in the midline, make an effort to be sure that when you tie your knot the mass of the knot is right exactly between the muscles—so that, in other words, it does not go into the muscle bundle. It will exert any pressure from its size into the line of the incision. I think if you will take time to do that, you'll be surprised at the lessening amount of discomfort that your patient may mention to you.

—J. BROOKS HOFFMAN, MD, *Greenwich, CT*

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Refer to: Lowinger P: American and English addicts in the British system (Commentary). West J Med 125:415-419, Nov 1976

Commentary

American and English Addicts in the British System

PAUL LOWINGER, MD, *San Francisco*

THE MANAGEMENT of narcotic addiction in the United Kingdom is by now relatively well publicized among Americans concerned with drug abuse and heroin addiction. Information as well as misunderstandings about the British system are not a new development. There has been an interchange of addiction information between the two countries for many years and in 1962 an American study of the British system was published by Schur.[1] In 1972 the Vera Institute developed a plan[2] for an experiment in heroin maintenance in the United States based on the British model. Nonetheless, English addiction specialists have been cautious in offering recommendations for the United States.

Treatment of Drug Addiction in Britain

The British narcotic addiction and drug abuse problem has changed and so has their approach to control. The British system must be understood in the light of these changes. Recent figures (at the end of 1973) show 1,818 known narcotic addicts in the United Kingdom[3] and an estimated 100 unknown addicts in a population of 55,000,000. The known addicts are those on the register of the British Home Office while the unknown addicts are estimated from the 5 percent proportion of narcotic deaths among persons not on the register.[4] The addict population is proportional to the full range of social classes and there are very few nonwhite addicts.[5] Three out of four addicts are men; they are predominantly young, averaging 25 years of age; 80 percent live in the London area. The number in 1973 represents a major increase in British addiction, which was limited to 400 to 600 known addicts until the 1960's. The typical British addict from the First World War until the 1960's was middle-aged, middle class, most often a woman and frequently a health professional. The addiction was limited to narcotics and was often of therapeutic origin. This addict was usually maintained on prescribed narcotics and functioned in work and family life. In contrast the recent addict is a young male polydrug user in a drug subculture for whom participation in work and family life is difficult.[6]

The principles of the treatment of narcotic addiction in the United Kingdom were established by the Rolleston Committee in 1926 and were reaffirmed in 1961 by the first Brain Committee. These principles included the withdrawal of narcotics from addicts but also recognized the need of some addicts for maintenance narcotics. This program worked reasonably well until the number of known narcotic addicts went from 335 in 1955 to 927 in 1965 and 2,782 in 1968.[6] As a result a second Brain Committee reporting in 1965 made several procedural changes in the system in the next three years. The philosophy remained the same, that is addiction was a medical problem for which the addict was treated as an individual pa-

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tient. The problem of overprescribing by six or seven medical practitioners had led to considerable heroin on the illegal market in the mid-1960's so that the prescribing privilege for heroin and cocaine was restricted to a small number of consultant psychiatrists working in the drug abuse programs. Despite the restriction on prescribing heroin and cocaine, all British physicians retain the right to prescribe all other drugs including methadone and barbiturates for the maintenance or withdrawal of addicts. Of the first ambulatory drug treatment centers set up, 14 of the 20 were located in the London area.

The second Brain Committee established compulsory registration of addicts by medical doctors. The British Home Office, which is the enforcement agency of the government, had voluntarily registered addicts for many years but no statutory authority required the reporting of addicts until 1968. The second Brain Committee recommended compulsory treatment of addicts but this was rejected by Parliament.[7]

My visits to London in September 1972 and April 1973 included a review of present arrangements for the treatment, control and prevention of addiction. The total number of addicts as well as the number of new addicts had declined by 1969 and was stable by 1970-1974. The clinics reported that the system was working well, as did police and addicts. Despite the presence of illegal "Chinese" heroin from Hong Kong, the epidemic of teenage polydrug abuse appeared to be winding down.

A Local Treatment Center

My first visit to a drug abuse treatment center was to the one at St. Clement's Hospital, which is in a working class area of London's East End. This program has been the subject of a previous paper,[7] and has prepared its own reports.[8,9] The personnel operating the clinic were largely nurses and social workers, with the major direction of this clinic from a nurse who had been in charge from its inception in 1968. A consultant in psychiatry was the supervising medical person and a junior psychiatrist was there daily. Some of the addicts came in every two weeks and there was a home visiting program by nurses and case workers so that each of the addicts on the clinic roster was visited at least once a month and usually more often. The emphasis was on family treatment. In September 1972 there were 120 addicts enrolled in the clinic with 70 receiving maintenance narcotics. Among the 70 persons taking legal drugs, two thirds were receiving methadone, a third were receiving heroin and a few were receiving both. The daily supply of drugs was given to the patients at a pharmacy of their choice according to prescriptions which went by mail or messenger from the clinic to the pharmacist. Most of the methadone was in the form of ampuls to be used intravenously. Heroin was furnished as 10 mg tablets suitable for use in injection. Needles and sterile water were also provided. In the year after the clinics were established, they prescribed some cocaine and methadrine but both were discontinued finally in 1970. The addicts who were doing well spent little time at the clinic but those who were jobless, isolated, physically ill or more dependent spent considerable time at the clinic.

During 1972 the clinic had seen only one or two new narcotic addicts a month; however, in 1968 when the clinic opened, the intake was considerably higher. The new subjects received urine tests for narcotics and were not placed on maintenance levels narcotics if findings on these tests were negative. Positive findings on a urine test did not guarantee maintenance narcotic medication because a patient who did not show withdrawal symptoms was not considered to be addicted even in the presence of a urine test positive for narcotics and recent injection marks. The other crucial aspect of the prescription of maintenance narcotics was a test narcotic injection in the clinic under observation of the nursing staff. These procedures established addiction and showed that the prescribed narcotic dose was close to the need.

Structure of the British System

My next visit was to the offices of the Addiction Division of the Department of Health and Social Security. Two hours in their offices were valuable in the understanding of the overall control of addicts, the system, the services, the budget and the role of professionals. The Division is a professional and administrative consultation program of the National Health Service; however, the individual drug treatment centers are controlled by the psychiatrists and the staff at each clinic. Budgets for each of the drug treatment programs are provided by the Regional Hospital Boards or by the Board of Governors in the case of medical school teaching hospitals. Each Regional Hospital Board is responsible for planning and providing the hospital services for a population between 2 and 5 million, including the treatment of drug

addiction. In addition a number of voluntary organizations supported by local government and private funds run therapeutic communities and day centers such as Phoenix House and the Community Drug Project.

Coordination of public and private effort is of importance and a London Area Council for this purpose was formed in 1972. The Department of Health and Social Security felt that addiction was under control, pointing out that the number of addicts was 1,466 in 1969, 1,430 in 1970, 1,580 in 1971, 1,619 in 1972 and 1,818 in 1973. Every effort was being made by the London clinics to reduce heroin prescribing so that the use of legal heroin went down from 1968 to 1974 while the amount of prescribed methadone increased. The amount of legal heroin and methadone prescribed and used by patients was carefully audited through clinic, pharmacy and wholesale records.

The next visit was to the Community Drug Project[10] in London's East End. This was operated by social workers who offered day care to addicts enrolled in a maintenance program or who were not yet registered. Many of the clients used it because they were friendless, lonely, looking for a job and needed a place to go during the day. In the morning the clients often came in to use the "fixing room." This provided a fairly satisfactory and safe place where legally prescribed drugs could be injected. The major purpose of the Community Drug Project was to foster independence, family relationships, jobs and emotional support. Those addicts who were working and less in need of this kind of program came in the afternoon or evening after work for group sessions and counseling.

One of the more disturbed addicts who used the Community Drug Project facility and its services during the day was interviewed. He was a 40-year-old man who had been released from prison 11 years previously after finishing a seven-year sentence and had been unemployed since. One reason that he worked little was that when he did work less money would be given to his wife and children, from whom he was separated. In addition he had a leg severely affected by cellulitis induced by the injection of narcotics. He was receiving maintenance levels of drugs but felt that he was not getting enough and so bought barbiturates on the illegal market. The program was helping him make an arrangement so that money he earned could be used for himself and his new wife while his divorced wife and children received social benefits. He was supported and encouraged to pursue treatment of the celluitis of his leg. It was hoped that the social support would lessen his need for illegal drugs and eventually permit him to reduce his prescribed heroin and methadone.

Another visit was to Dr. Peter Chapple, a psychiatrist, and his National Addiction and Research Institute in the Kensington-Chelsea section of London. Dr. Chapple's nongovernmental program was interested in the withdrawal of patients from narcotic addiction rather than in maintenance. The program used oral administration of methadone for ten days to six weeks and support was provided by exaddicts serving as counselors in a day-care setting. Dr. Chapple had been a public critic of the second Brain Committee regulations. He remained critical of the high maintenance doses prescribed in the government clinics, nonetheless he prefers the present British system to any other plan. He points out that British laws governing drug abuse have become more punitive in the last five years as the government and the public have become more frightened. He feels that punitive legislation restricts personal rights, glamorizes the drug culture and promotes the illegal market.

The Role of Pharmacies

A morning was spent in one of the special pharmacies which was permitted to fill clinic narcotic prescriptions. Mr. Basu, the pharmacist, was helpful to the addicts who came in for their daily supply of prescribed narcotics and by noon most of the customers in the store were addicts. This pharmacy had served addicts for 15 years in the Camberwell area and as a result some nonaddict patients prefer to use other pharmacies. Nonetheless the pharmacist regarded helping addicts as a public service. He estimated that a third of his business was the filling of narcotic prescriptions from government clinics. Of course, in the British health system each addict paid only a 25 cent service charge for each prescription rather than the full value. This drugstore which was privately owned was decorous and pleasant. The addicts knew the pharmacist and there was a good rapport. While I was visiting, the pharmacist arranged an escort for an addict who was "sick" from withdrawal symptoms. A week's prescription for a female addict was noted: 168 tablets of 10 mg heroin, 21 ampuls of 10 mg injectable

methadone and 14 capsules of 100 mg Seconal® (secobarbital).

Despite the legality of narcotic prescription for registered addicts, there was a "copping" scene. A pound ($2.50 at the time) could buy a 10 mg heroin tablet or six Tuinal® (secobarbital) capsules or a packet of "Chinese" heroin. Addicts not using legal narcotics often used two to five packets a day of the dilute "Chinese" heroin in order to prevent withdrawal symptoms.

A visit to the Institute of Drug Dependence at Chandos House in London provided a chance to talk with Jasper Woodcock, a social scientist who was conversant with the range of British addiction research. This led to a conversation with Zacune who studied Canadian narcotic addicts in Great Britain and Canada.[11] Canadian narcotic addicts living in London do as well as British addicts with respect to employment, crime and social functioning. These Canadian addicts had a much worse record in Canada before they came to live in England between 1959 and 1964 in order to obtain legal narcotics. The sample of 25 Canadian addicts spent a total of 141 years in prison in Canada, an average of 5.6 years per addict, so that 41 percent of their 13.3 addicted years in Canada were spent in prison. During their average of 5.8 years in Britain they spent an average of one month per addict or only 2 percent of their time in prison. Only one of these addicts worked steadily during their addicted years in Canada while 13 of the 25 were fully employed in England. This study has importance because the Canadian system is similar to that in the United States—that is, there is no maintenance use of heroin so that all heroin used by addicts is illegal.

American Addicts in London

That there were 20 to 30 addicts from the United States in London was an observation of Klein[12] and was confirmed in my talk with Zacune. This led me to interview several American addicts for a pilot report.

Five addicts who were born and also had become addicted to narcotics in the United States and who now live in England were interviewed. They were all white men in their thirties or early forties. All were receiving maintenance levels of narcotics through London clinics as part of the national health plan.

A typical subject was a 35-year-old man who was born in Boston. He had used narcotics for 20 years, spending the first 10 of his addicted years in the United States and the last 10 years in London. In the United States he had served two separate prison sentences amounting to five years and was also admitted to hospitals and withdrawn from narcotics on two occasions. At the time he left the United States in 1962 he was spending $10 to buy one grain of heroin daily. He was on maintenance during his ten years in London and is presently receiving five grains of heroin, 12 ampuls of 10 mg injectable methadone and 10 tablets of 10 mg methadone per day. He has worked fairly regularly in England. His work record in the United States was poor by comparison because of the time spent in finding narcotics or undergoing withdrawal when he was without narcotics as well as the difficulty getting work with a criminal record. He has used barbiturates sporadically throughout his addicted years and at the time he was interviewed in London, he was in the hospital recovering from an excess use of a barbiturate, Tuinal, which he acquired on the illegal market.

His first marriage broke up at the age of 22 when he was unable to support his wife because he spent all his money on narcotics. He separated from his second wife in 1973 because she became interested in another man. As a result of the break up of this marriage he had a new girlfriend whom he had planned to marry. It was in this period of turmoil about his forthcoming divorce and marriage that he resumed the use of Tuinal which led to the admission to hospital. He prefers the English system with its provision for maintenance levels of narcotics. He feels that if he had remained in the United States he would have eventually served a long prison sentence for use, possession or sale of narcotics and might have died of an overdose, as have many of his American friends. It has been easy to be active in his career in England but this would have been almost impossible in the United States. The other four addicts from the United States were similarly more successful in London on maintenance narcotics. It must be kept in mind that the North American addicts who live in England are not typical of the addicts who stayed in North America and that the later years during a life of addiction may be more benign than the earlier years.

How Well Does the British System Work?

The amount of success of the British system was a frequent question during my London visits. One answer is a recent follow-up study of Eng-

lish addicts receiving maintenance levels of narcotics by Chapple.[13,14] He reported on a group of 108 London addicts with follow-up for six to seven years:

"23 percent were off opiates, legal and illegal; did not use other drugs; kept a regular job; received education and had stable personal relationships.

"18 percent died—this is 2 to 3 percent a year or more than 20 times the normal mortality rate for this age group; 'overdose' accounted for most of these deaths but the term included massive doses, negative tolerance, allergic reaction, etc.

"32 percent remained on legal prescription with decrease in the number on heroin and the majority on methadone.

"7 percent were in jail or the hospital.

"20 percent remained unaccounted for."

Summary

Heroin maintenance merits serious consideration in the United States based on experience in England with English as well as Canadian and American addicts. British narcotic policies offer a medical approach to addicts in contrast with the United States where the approach is frequently punitive.

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Correlation of Parathyroid Size and Serum Calcium Level

You all know that the size of a hyperparathyroid tumor in the neck is roughly proportionate to the elevation of calcium. And if you find a small tumor abnormality during operation and the patient's calcium level is 16 mg per 100 ml, be wary. There is another mass of abnormally functioning parathyroid tissue someplace. At least, by inference, there may well be. So don't get trapped there.

—WILLIAM O. BARNETT, MD, *Jackson, MS*
Extracted from *Audio-Digest Surgery*, Vol. 22, No. 18 in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Peer Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Peer Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Peer Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Gynecomastia

QUESTION:

Please indicate which of the listed conditions are, in your opinion, medically necessary, which are cosmetic and which require that the question of medical necessity be resolved through individual case review?

I. Gynecomastia associated with demonstrable endocrine dysfunction
- *A. Medical treatment*
- *B. Surgical treatment to breast area*
  - *1. Adipose hyperplasia*
  - *2. Mammary gland hyperplasia*

II. Adolescent gynecomastia, ages 12 to 20
- *A. Unilateral*
- *B. Bilateral*

III. Adult gynecomastia
- *A. Unilateral*
- *B. Bilateral*

IV. Pseudogynecomastia
- *A. Unilateral*
- *B. Bilateral*

(Asked by the California Department of Health)

OPINION:

In the opinion of the Advisory Panels on General Surgery, Internal Medicine and Plastic Surgery, operations for gynecomastia are not generally considered cosmetic.

Panel members felt that patients with demonstrable hormonal dysfunction should be treated medically and the dysfunction corrected before surgical operation is considered, as the gynecomastia may subside spontaneously.

Both adult and adolescent unilateral and bilateral gynecomastia are abnormal conditions sometimes marked by tenderness, inflammation or malignancy. In some cases biopsy studies would be necessary to establish a diagnosis. In patients with gynecomastia resultant psychological problems frequently are present. The panels generally agreed that surgical treatment would be necessary and appropriate for such patients even though the condition, while abnormal, is not health-threatening or life-threatening.

Indications for Total Hip Replacement

QUESTION:

Please list the indications for total hip replacement in the presence of an acute fracture of the proximal end of the femur. (Asked by Mercy Hospital, San Diego)

OPINION:

In the opinion of the Advisory Panel on Orthopedics, total hip replacement may be indicated for a patient with an acute fracture of the proximal end of the femur when in the judgment of the orthopedic surgeon the replacement operation will give a better functional result than simple healing of the fracture.

Such circumstances might include patients with severe preexisting arthritis or osteoporosis involving the femoral head or acetabulum or both; patients with an extensive fracture of the acetabulum or proximal femur which would require replacement of the femoral head, or patients with other malformation or abnormality of the hip joint which would have been an indication for future hip replacement.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

HYPNOSIS IN THE RELIEF OF PAIN—Ernest R. Hilgard, PhD, and Josephine R. Hilgard, MD, PhD, Stanford University. William Kaufmann, Inc., One First Street, Los Altos, CA (94022), 1975. 262 pages, $12.50.

Among the most ancient threads in the historic fabric of the healing professions are both pain in its variegated and oft mysterious forms, and hypnosis as applied in its numerous guises (for example, laying on of the hands, the Aesculapean Temple's rest cures and the like).

In the first section of their book, the Hilgards have most successfully woven these threads together by first elucidating the history and current understanding of each phenomenon and then describing the tremendous potential applicability of hypnotic technique in the control and alleviation of pain.

The second section deals with specific applications under the general heading of pain as it occurs with cancer, obstetrics, surgical procedures and dentistry. The concluding chapters deal with hidden pain and its interpretation and the future of hynosis in pain control.

In all, the book is well written and most understandable regardless of the reader's level of sophistication in neurophysiology, psychiatry or experimental protocol. It is made understandable particularly because of the summary of salient points and highly annotated comments contained at the conclusion of each chapter.

There is only one note of regret reflected in the book and that is that there are far too few practitioners who avail themselves of the unique and specific opportunity to utilize the efficacy of the hypnotherapeutic techniques in the alleviation of their patients' experience of pain. This book makes a major contribution, through its careful explanations and balanced presentation, toward righting this situation.

SHELDON KARDENER, MD, FASCH
Department of Psychiatry
UCLA School of Medicine

URBAN ENTOMOLOGY—Walter Ebeling, PhD, Professor of Entomology and Entomologist in the Experiment Station, University of California, Los Angeles. University of California, Berkeley, Division of Agricultural Sciences, 1422 South Tenth Street, Richmond, CA (94804), 1975. 695 pages, $27.50 plus applicable State sales tax.

For years it has been apparent to many that when man has passed from the face of the earth, his immediate successor will be the insect family. Insects have assured their future by their overwhelming ability to reproduce and adapt to man's world. These ubiquitous creatures have become so much a part of our everyday life that they are largely ignored, and have even been assimilated into our colloquialisms. From a more practical standpoint, insects have enormous social, economic and medical impact. Their role as vectors in the dissemination of infectious diseases is well documented. The considerable outlays of time, research and money for development of more potent pesticides have, in and of themselves, recently posed serious health questions.

Urban Entomology by Professor Walter Ebeling of the Department of Entomology at the University of California, Los Angeles is not written specifically for physicians or allied health personnel, but it encompasses a multitude of public health service problems. The book discusses governmental agencies and legislation dealing with pest controls; pesticides—their use and potential complications; infestations of food, water and clothing; vertebrate and nonvertebrate pests attacking man, and even delusionary parasitosis (patients who suffer from delusions that they are being parasitized by insects).

For students of public health, this book provides explicit information about the habitats of various insects and the relationship of these habitats to their role as vectors in the dissemination of disease. The chapters entitled "Pests Attacking Man and His Pets" and "Vertebrate Pests Such as Rodents, Bats and Birds" deal with more specific instances of patient care for a variety of situations ranging from the common to the unusual. The recognition, emergency and definitive management of venomous stings and bites, in addition to an understanding of the pathophysiology outlined in these chapters, constitute essential information for every emergency physician as well as many pediatricians and surgeons. Dr. Ebeling points out the relative dangers of each species of venomous creatures; for example, from 1950 to 1959, of 400 deaths reported secondary to envenomation, 230 were caused by anaphylaxis secondary to hymenopterism as compared with 94 deaths caused by rattlesnake bites.

The text is generously illustrated with colored and black-and-white photographs of venomous insects, arthropods and reptiles. The individual pests can be readily identified by habitat, potency, mode of envenomation and region of the country where they are generally found. Beyond this, the author outlines the usual symptom complexes caused by various venomous pests and points out the physiology behind emergency and other definitive therapy. He describes specific pests that constitute medical nuisances because of their venom and conveniently provides useful data concerning infectious diseases and the insect's role in their causation. The text serves as an invaluable addition to our emergency room reference shelf; it is an excellent source of information for physician and student alike.

MARK E. JERGENS, MD
UCLA Emergency Medical Center
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DISEASES OF THE NOSE, THROAT AND EAR—A Handbook for Student and Practitioners: Eleventh Edition—I. Simson Hall, MB, ChB, FRCPEd, FRCSEd, Consulting Surgeon, the Royal Infirmary, Edinburgh, Lecturer Emeritus in Diseases of Nose, Throat and Ear, University of Edinburgh; and Bernard H. Colman, MA, MSc, ChM, FRCSEd, Senior Surgeon, Department of Otolaryngology, the Radcliffe Infirmary, Oxford, Clinical Lecturer in Otolaryngology, University of Oxford. Churchill Livingstone Medical Divison, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 352 pages, $12.50 (Softbound).

The original edition of this handbook was published in 1937, designed for the needs of medical students and general practitioners. It continues to be so oriented in its eleventh edition. Unfortunately, as is so often the case with old textbooks, the revisions are quite inadequate. Much of the book remains archaic and the updating is sparse and spotty. Consequently this rather attractive little book cannot be recommended either as a text or reference book for students or general practitioners. Fortunately, many more adequate texts in this field are available.

CHARLES P. LEBO, MD

in memoriam

Ancona, Giacomo, San Francisco. Died September 2, 1976, aged 89. Graduate of Regia Università degli Studi di Firenze, Facoltà di Medicina e Chirurgia, 1912. Licensed in California in 1940. Dr. Ancona was a member of the San Francisco Medical Society.

Austin, William E., San Francisco. Died February 6, 1976 of leukemia, aged 65. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1946. Licensed in California in 1950. Dr. Austin was a member of the San Francisco Medical Society.

Barber, Dale Emerson, Napa. Died September 28, 1976 in Napa of myocardial infarction, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Dr. Barber was a member of the Napa County Medical Society.

Bates, Osmund George, San Francisco. Died September 14, 1976 in San Francisco, aged 66. Graduate of Harvard Medical School, Boston, 1935. Licensed in California in 1939. Dr. Bates was a retired member of the San Francisco Medical Society.

Chinn, Silas, Fresno. Died September 4, 1976, aged 60. Graduate of the University of California Medical School, Berkeley-San Francisco, 1941. Licensed in California in 1941. Dr. Chinn was a member of the Fresno-Madera Medical Society.

Corp, Keith W., Salinas. Died September 18, 1976 in Salinas, aged 67. Graduate of the University of Nebraska College of Medicine, Omaha, 1939. Licensed in California in 1940. Dr. Corp was a retired member of the Monterey County Medical Society.

Cosgrove, Jay B., Los Angeles. Died August 24, 1976 in Los Angeles of heart disease, aged 71. Graduate of Northwestern University Medical School, Chicago, 1930. Licensed in California in 1930. Dr. Cosgrove was a member of the Los Angeles County Medical Association.

Felmus, Richard Dexter, Beverly Hills. Died August 23, 1976 in Beverly Hills of heart disease, aged 62. Graduate of Long Island College of Medicine, New York, 1942. Licensed in California in 1949. Dr. Felmus was a member of the Los Angeles County Medical Association.

Fitzhugh, William McPherson, Pebble Beach. Died September 19, 1976 in Pebble Beach, aged 75. Graduate of McGill University Faculty of Medicine, Montreal, 1933. Licensed in California in 1934. Dr. Fitzhugh was a retired member of the Monterey County Medical Society.

Gardner, Arthur Floyd, Long Beach. Died August 31, 1976 in Long Beach of chronic obstructive lung disease, aged 78. Graduate of New York University College of Medicine, New York, 1929. Licensed in California in 1933. Dr. Gardner was a member of the Los Angeles County Medical Association.

Goodwin, Robert, Van Nuys. Died August 17, 1976 in Los Angeles of complications of surgical operation, aged 50. Graduate of Georgetown University School of Medicine, Washington DC, 1952. Licensed in California in 1954. Dr. Goodwin was a member of the Los Angeles County Medical Association.

Hoffman, Arthur Max, Beverly Hills. Died August 4, 1976 in Los Angeles of esophageal carcinoma, aged 78. Graduate of Harvard Medical School, Boston, 1922. Licensed in California in 1924. Dr. Hoffman was a member of the Los Angeles County Medical Association.

Holcomb, William Frederick, Oakland. Died September 4, 1976 in Oakland of heart disease, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1924. Dr. Holcomb was a retired member of the Alameda-Contra Costa Medical Association.

Kennedy, William John, Oakland. Died August 21, 1976 in Oakland of renal and respiratory failure, aged 68. Graduate of the University of Cincinnati College of Medicine, 1934. Licensed in California in 1935. Dr. Kennedy was a member of the Alameda-Contra Costa County Medical Association.

Kern, Arthur, Bell Gardens. Died July 25, 1976 of heart disease, aged 67. Graduate of the Chicago College of Osteopathy, 1949. Licensed in California in 1949. MD degree from California College of Medicine, 1962. Dr. Kern was a member of the Los Angeles County Medical Association.

Kincses, Janos, Long Beach. Died September 2, 1976 in Long Beach of metastatic adenocarcinoma, aged 71. Graduate of Magyar Királyi Erzsébet Tudományegetyetem Orvostudományi, Pécs, Hungary, 1929. Licensed in California in 1952. Dr. Kincses was a member of the Los Angeles County Medical Association.

Manzone, Peter Victor, San Francisco. Died September 4, 1976 in San Francisco, aged 68. Graduate of Regia Università di Torino, Facoltà di Medicina e Chirurgia, 1932. Licensed in California in 1949. Dr. Manzone was a member of the San Francisco Medical Society.

McCarthy, William D., Oakland. Died September 21, 1976 in Oakland of acute leukemia, aged 68. Graduate of Cornell University Medical College, New York, 1935. Licensed in California in 1942. Dr. McCarthy was a member of the Alameda-Contra Costa Medical Association.

MOHUN, MEADE, San Mateo. Died September 11, 1976, aged 77. Graduate of the University of Nebraska College of Medicine, Omaha, 1927. Licensed in California in 1930. Dr. Mohun was a member of the San Mateo County Medical Society.

REYNOLDS, AUDREY H., Stockton. Died August 30, 1976 in Stockton, aged 51. Graduate of Northwestern University Medical School, Chicago, 1954. Licensed in California in 1955. Dr. Reynolds was a member of the San Joaquin County Medical Society.

SCHORR, RICHARD, Los Angeles. Died July 28, 1976 in Los Angeles of heart disease, aged 76. Graduate of the University of Maryland School of Medicine, Baltimore, 1923. Licensed in California in 1946. Dr. Schorr was a member of the Los Angeles County Medical Association.

SEIFERT, EDWIN ANDREW, San Francisco. Died September 9, 1976, aged 76. Graduate of the Ohio State University College of Medicine, Columbus, 1924. Licensed in California in 1962. Dr. Seifert was a member of the San Francisco Medical Society.

STARR, HARVEY EVERETT, Los Angeles. Died July 13, 1976 in Los Angeles of carcinoma, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1935. Dr. Starr was a member of the Los Angeles County Medical Association.

THOMAS, OWEN F., Santa Rosa. Died September 4, 1976 in Santa Rosa of carcinoma of the pancreas, aged 61. Graduate of the University of Colorado School of Medicine, Denver, 1940. Licensed in California in 1948. Dr. Thomas was a member of the Sonoma County Medical Association.

VRCON, STANLEY, San Francisco. Died July 2, 1976, aged 62. Graduate of Regia Università degli Studi di Padova, Facoltà di Medicina e Chirurgia, 1943. Licensed in California in 1955. Dr. Vrcon was a member of the San Francisco Medical Society.

WILLIAMS, WALTER, Los Angeles. Died April 26, 1976 in Los Angeles of Parkinson's disease, aged 77. Graduate of Medizinische Fakultät der Universität, Heidelberg, 1922. Licensed in California in 1937. Dr. Williams was a retired member of the Los Angeles County Medical Association.

WILSON, FRANK M., Van Nuys. Died August 21, 1976 in Woodland Hills of heart disease, aged 77. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1917. Licensed in California in 1919. MD degree from California College of Medicine, 1962. Dr. Wilson was a member of the Los Angeles County Medical Association.

Full meeting schedule in December issue
The Western Journal of Medicine

106th Annual Session

March 4-9, 1977 • Disneyland Hotel, Anaheim

PLAN TO ATTEND

PROGRAMS

- Lung cancer
- Ophthalmic oncology
- Allergic lung disease
- Salivary gland tumors
- Nuclear medicine in cardiovascular disease
- Pulmonary intensive care medicine
- Surgical infections and antibiotics
- Environmental pathology
- Primary care and occupational medicine
- Pediatric infectous disease
- OB topics: estrogens; home deliveries
- Regionalization of perinatal care
- CAT scanning
- Urology and endocrinology
- Herpes simplex
- Chronic low back pain
- Controversies in psychiatric treatment
- Psychopharmacology
- The medical family in crisis
- Health instruction in public schools

AFFILIATED MEETINGS

- American Cancer Society, California Division
- California Association of Ophthalmology
- California Association of Neurological Surgeons
- California Section of the American College of Obstetricians and Gynecologists
- California Society for the Treatment of Alcoholism and Other Drug Dependencies
- California Society of Allergy and Clinical Immunology
- California Tumor Tissue Registry
- California District, American Academy of Pediatrics
- California Society of Physical Medicine and Rehabilitation

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47th Annual Convention—California Medical Association Auxiliary

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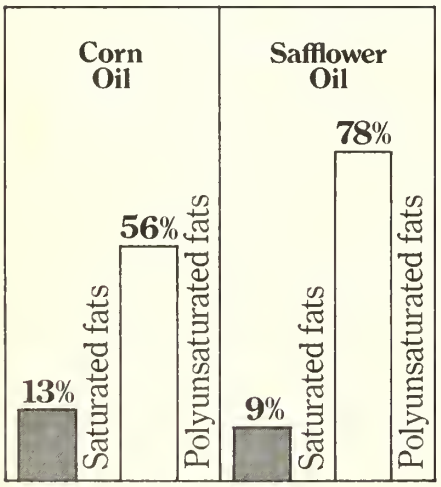

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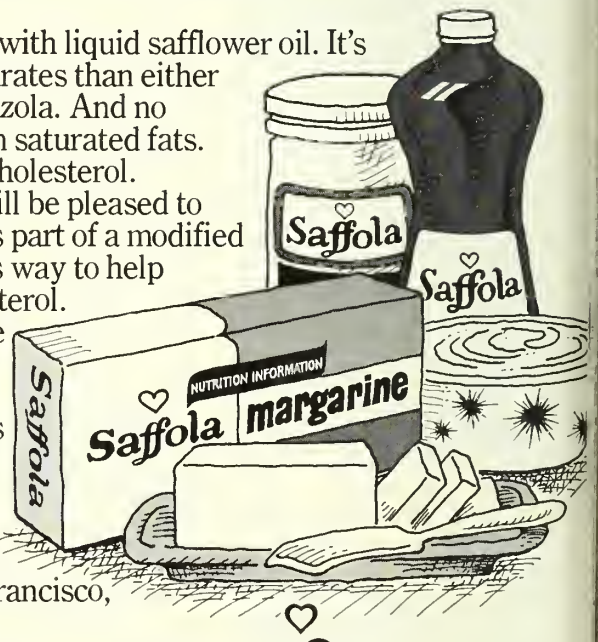

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Pain: a call to action.

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- ☐ one tablet q.6 h.*

Percodan® Tablets

Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine (II)

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

SCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning: May be habit forming), 0.38 mg. oxycodone terephthalate (Warning: May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN*, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN* is subject to the Federal Controlled Substances Act.

Operation ambulatory patients Oxycodone may impair the mental and physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN* should be cautioned accordingly.

Concomitant with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN* may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN* should not be used in pregnant women unless in the judgment of the physician, the potential benefits outweigh the possible hazards.

Use in children PERCODAN* should not be administered to children. PERCODAN*-Demi, containing half the amount of oxycodone, can be considered. (See product prescribing information for PERCODAN*-Demi.)

Opiates should be used with caution in the presence of peptic ulcer, coagulation abnormalities.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN* or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN* should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may be occasionally necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN* is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN* may be additive with that of other CNS depressants. See WARNINGS.

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents.

MANAGEMENT OF OVERDOSAGE Signs and Symptoms Serious overdose with PERCODAN* is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN* may, in addition, result in acute salicylate intoxication.

Treatment Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

DEA Order Form Required

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Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

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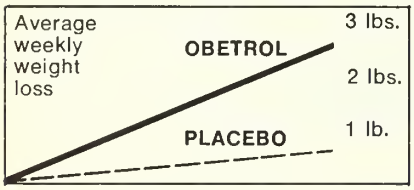

Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant tas diarrhea, other gastrointestinal disturbances. Anorexia a weight loss may occur as undesirable effects when amphe mines are used for other than the anorectic effect. *Allerg* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphe mines should be administered at the lowest effective dosa and dosage should be individually adjusted. Late evening me cation should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams da raised in increments of 2.5 milligrams at weekly intervals u optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once twice daily, increased in increments of 5 milligrams at wee intervals. Only in rare cases will it be necessary to exceed total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day divided doses.

Overdosage: Manifestations of acute overdosage with amphe mines include restlessness, confusion, assaultiveness, hall nations, panic states. Fatigue and depression usually fol the central stimulation. Cardiovascular effects include arrh mias, hypertension or hypotension, and circulatory collap Gastrointestinal symptoms include nausea, vomiting, diarrh and abdominal cramps. Fatal poisoning usually terminates convulsions and coma.

Management of acute amphetamine intoxication is larg symptomatic and includes lavage and sedation with a barb rate. Experience with hemodialysis or peritoneal dialysis inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets

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January 1

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consider the effect on coexisting diabetes when you prescribe a vasodilator*

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ıbetic patient has been reported with

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(ISOXSUPRINE HCl)

ALETS, 20 mg.

le compatible vasodilator

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***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

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(Contnued on Page 32)

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(Continued from Page 30)

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EMERGENCY PHYSICIANS: Continue to live at home; supplement your income while commuting to our nationwide locations. Scheduling flexible —weekends, weekly or monthly—part-time, locum tenens or full-time. Commuting allowance, paid malpractice and state license fees; excellent remuneration. Contact Drs. Cooper, Spurgeon or Greenberg toll free 1-800-325-3982 for details.

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PRIMARY CARE PHYSICIAN, WEEKEND COVERAGE, hospital-based, some week nights, excellent salary ($3,000-$4,000 per month), no overhead, challenging opportunity, immediate placement, send c.v. to Barbara Rice, Central Orange County Medical Group, 450 N. Roxbury Drive, Suite 604, Beverly Hills, CA 90210.

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FAMILY PRACTICE AND/OR OB/GYN. Small growing community, diversified economic base, pleasant hospital, no investment, excellent fringe benefits, financial reimbursement open, just take over practice, no malpractice threats, any kind of recreational source nearby. Call or write Fillmore Hospital, Richard Packer, 25 South 100 West, Fillmore, Utah 84631; (801) 743-5400.

PHYSICIANS NEEDED—BY ESTABLISHED CALIFORNIA GROUPS, Internists with subspecialties of Oncology-Hematology-Pulmonary or Rheumatology. Also Orthopedic Surgeon-Obstetrician/Gynecologist and General Practitioner. Malpractice and Agency fee paid by Medical Groups. Phone Norma Rohl, Director, (415) 982-3412, Medical Center Agency, 870 Market St., San Francisco 94102.

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(Continued on Page 40)

APPALACHIAN REGIONAL HOSPITALS

Malpractice Insurance Problems?—You are Needed In Appalachia

A rural regional health care system located in the beautiful mountains of Eastern Kentucky, Virginia and West Virginia needs Family Practitioners, OB-GYN, Radiologists, Psychiatrists, ENT, General Surgeon, Internists and specialists in Emergency Medicine for its ten (10) hospitals and Primary Care Centers. ARH provides comprehensive health and health related services to a major segment of rural Appalachia. Excellent starting salaries and fringe benefits include malpractice insurance, four (4) weeks paid vacation, paid health insurance, and moving expenses.

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NONINVASIVE METHODS FOR THE NURSE/TECHNICIAN

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24 hours Category I Credit, 5-day conference at the Maui Surf Hotel, February 21-25, 1977: **ADVANCES IN PATIENT CARE.** Write or call for agenda and details, 315 University District Bldg., 1107 N.E. 45th St., Seattle, Washington 98105. (206) 633-0505.

CLASSIFIED INFORMATION CALL (415) 777-2000

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CANCER

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December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** California Tumor Tissue Registry at Century Plaza Hotel, Los Angeles. Sunday. 6 hrs. $100. Contact: CTTR, 1200 N. State St., Box 40, Los Angeles 90033. (213) 226-4614.

December 29-30—**Clinical Cancer Symposium.** USC. Wednesday-Thursday.

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MEDICINE

November 27-29—**Advances in Heart Disease—1977.** American College of Cardiology at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

November 29-December 3—**Advances in Diagnosis and Treatment in Clinical Medicine.** American College of Physicians at Queensway Hilton Hotel, Long Beach. 27 hrs. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

December 2-3—**Respiratory Failure Workshop.** USC. Wednesday-Friday.

December 8-10—**Respiratory Failure Workshop.** USC at Canyon Hotel, Palm Springs. Wednesday-Friday.

December 11—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. $250.

January 3-June 27—**Internal Medicine Board Review Course.** UCSD at University Hospital, San Diego. Monday evenings. 75 hrs.

January 14-15—**Identification of the Fifty Common Dermatoses.** UCSF. Friday-Saturday.

January 15—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

January 17-20—**Ischemic Heart Disease Problems and Perspectives.** Univ. of Hawaii School of Medicine, American Heart Assn., Hawaii Heart Assn. at Royal Lahaina Hotel, Maui, Hawaii. Monday-Thursday. 13 hrs. $175. Contact: Hawaii Conference Services, P.O. Box 22679, Honolulu 96822.

January 21-23—**Advances and Controversies in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda MD 20014.

January 22-23—**Dermatologic Surgery.** See Surgery, January 22-23.

January 23-29—**Topics in Internal Medicine—2nd Annual** UCSD at Town and Country Hotel, San Diego. One week.

January 24-26—**Cardiac Auscultation.** American College of Physicians at LLU. Monday-Wednesday. 18 hrs. Contact: Registrar of Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 26-28—**Advances in Neurology.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

February 13-17—**Pulmonary Medicine.** UCSF at Lake Tahoe. Sunday-Thursday.

February 14-19—**Pediatric Nephrology.** See Pediatrics, February 14-19.

February 16-18—**Recent Advances in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 18-19—**Dermatotoxicology.** UCSF. Friday-Saturday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

OBSTETRICS AND GYNECOLOGY

January 6-June 30—**Ob-Gyn Review.** UCLA. Thursdays.

January 13-14—**Current Concepts in Prenatal Diagnosis.** UCSD at Hilton Hotel, San Diego. Thursday-Friday.

January 14—**Infections and Septic Shock in Obstetrics and Gynecology.** California Hospital Medical Center, Los Angeles. Friday. 5½ hrs. $15. Contact: Keith P. Russell, MD, Dir., Ob-Gyn Resident Training Program, CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

January 29-February 5—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

February 5-6—**Ob-Gyn Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Miss Dee Davis, Exec. Sec., Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 7-11—**Obstetrical and Gynecological Assembly of Southern California.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Monday-Friday. Contact: Miss Dee Davis, Exec. Sec., Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 17-19—**Neonatology.** USC. Thursday-Saturday.

PEDIATRICS

December 2-4—**General Pediatrics.** American Academy of Pediatrics at Monterey. Thursday-Saturday. Contact: Gerald E. Hughes, MD, AAP, P.O. Box 1034, Evanston, Ill. 60204. (312) 869-4255.

December 4—**American Academy of Pediatrics, California Chapter I, District IX.** San Francisco. Saturday. Contact: Melvin H. Schwartz, MD, 2219 Santa Clara Ave., Alameda 94501.

January 13-16—**Ski and Study Symposium—2nd Annual.** American Academy of Pediatrics, California Chapter 2, at Mammoth Mountain. Thursday-Sunday. 14½ hrs. $125. Contact: AAP, Calif. Chapter 2, P.O. Box 2134, Inglewood 90305.

January 22-23—**Pediatric Urologic Seminar.** Children's Hospital of Los Angeles. Saturday-Sunday. Contact: H. H. Edelbrock, MD, Program Dir., CHLA, P.O. Box 85544, Los Angeles 90027.

January 28-30—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 28-30.

February 3-5—**Adolescent Medicine.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday. 21 hrs.

February 14-19—**Pediatric Nephrology.** UCSD at Vacation Village, San Diego. Monday-Saturday.

PSYCHIATRY

December 2-5—**Treatment of Sexual Dysfunctions.** See Of Interest To All, December 2-5.

January 4-March 15—**Intensive Review of Psychiatry and Neurology.** USC. Tuesdays. 40 hrs.

January 30-February 4—**Mid-Winter Program for Psychiatrists—3rd Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 11-12—**Adolescence Today: Psychosocial Issues—3rd National Seminar.** Vista Hill Foundation and Sharp Memorial Hospital at Hotel del Coronado, Coronado. Friday-Saturday. 10 hrs. $65. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

RADIOLOGY AND PATHOLOGY

December 12—**Slide Seminar on Tumors and Tumor-Like Conditions of the Lymphoreticular and Hematopoietic Systems.** See Cancer, December 12.

The Medical Staff of Daniel Freeman Hospital

Presents

The 6th Annual Symposium

CURRENT TRENDS IN CANCER THERAPY

Friday, December 10, 1976 • 8:15 a.m.-4:30 p.m.
Saturday, December 11, 1976 • 8:15 a.m.-12 Noon

LOS ANGELES MARRIOTT HOTEL
5855 West Century Blvd., Los Angeles, CA 90045
(Adjacent to Los Angeles International Airport)

Symposium Course Director: Elliott Hinkes, MD, Director of Oncology/Hematology, Daniel Freeman Hospital. Assistant Clinical Professor, Medicine, School of Medicine, University of California, Los Angeles.

The Symposium is a two-day course of current trends in the management of the patient with cancer. Emphasis will be placed on **practical clinical** aspects of cancer management.

Course Objectives: To familiarize the physician and surgeon who sees the cancer patient with the following topics:

- Segmental mastectomy in selected patients with primary breast cancer—an alternative to radical surgery.
- Radiation therapy as an alternative to radical prostatectomy in primary prostatic cancer.
- Adjuvant chemotherapy—the rationale of post-operative chemotherapy in various solid tumors with emphasis on breast cancer. Should all patients with cancer be treated after surgery?
- Radiologic and therapeutic advances in cancer—EMI scans, body scans, xeromammography, linear accelerator therapy, etc.
- Newest advances in leukemias and lymphomas, including bone marrow transplantations—are some patients curable?
- Immunotherapy—the newest tool for cancer control?

GUEST FACULTY:

MARTIN J. CLINE, M.D., The Bowyer Professor of Medical Oncology; Chief, Division of Hematology-Oncology; Director of Medical Oncology, School of Medicine, University of California, Los Angeles

BERNARD FISHER, M.D., Professor of Surgery, University of Pittsburgh School of Medicine; Director, National Surgical Adjuvant Breast Project, Pittsburgh, Pennsylvania

DONALD MORTON, M.D., Chief, Division of Oncology; Professor of Surgery, School of Medicine, University of California, Los Angeles; Chief, Oncology Section, Surgical Service, Veteran's Administration Hospital, Sepulveda

SAUL ROSENBERG, M.D., Chief, Division of Oncology, Professor of Medicine and Radiology, Stanford University School of Medicine, Stanford, California

DANIEL FREEMAN HOSPITAL FACULTY:

LAWRENCE BIRNBAUM, M.D., Chairman, Plastic Surgery Department, Daniel Freeman Hospital; Instructor, Plastic Surgery Department, School of Medicine, University of Southern California

ELLIOTT HINKES, M.D., Director of Oncology/Hematology, Daniel Freeman Hospital; Assistant Clinical Professor, Medicine, School of Medicine, University of California, Los Angeles

ARTHUR F. SCHANCHE, M.D., Chief of Radiology, Daniel Freeman Hospital, Assistant Clinical Professor, Radiology, School of Medicine, University of California, Los Angeles

RICHARD SMALL, M.D., Director of Radiation Oncology Department, Daniel Freeman Hospital; Assistant Professor, Radiology/Radiation Therapy, School of Medicine, University of California, Los Angeles

Course Coordinator: Donald A. Dennis, PhD, Director of Medical Education, Daniel Freeman Hospital

REGISTRATION FEE:

$85.00 (includes one luncheon, refreshments and pass-out materials).

Make checks payable to:
Department of Medical Education, 1976 Symposium

Mail to: Department of Medical Education
Daniel Freeman Hospital
P.O. Box 100, Inglewood, CA 90306

Telephone: (213) 674-7050, Ext. 127-128

CREDIT: This is an approved program of continuing medical education. Physicians attending this course may report up to 9 hours of Formal (Category 1) credit towards the California Medical Association Certificate in Continuing Medical Education and the American Medical Association Physician Recognition Award.

1977 Winter Conference Schedule

BETH ISRAEL HOSPITAL DENVER, COLORADO

JANUARY 22 TO JANUARY 29, 1977
Vail Internal Medicine Conference
FEBRUARY 12 TO FEBRUARY 19, 1977
Vail Family/General Practice Conference
FEBRUARY 19 TO FEBRUARY 26, 1977
Vail OB/GYN Conference
FEBRUARY 26 TO MARCH 5, 1977
Aspen Radiology Conference
MARCH 5 TO MARCH 12, 1977
Vail Psychiatry Conference
MARCH 12 TO MARCH 19, 1977
Vail General Surgery Conference

For registration information: Call or Write
Beth Israel Hospital Conference Program
1818 Gaylord St., Denver, CO 80206
(303) 320-5333

January 28-30—**Midwinter Radiological Conference—29th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Ronald W. Thompson, MD, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029.

January 28-30—**Radioimmunoassay Symposium.** UCSF. Friday-Sunday.

January 31-February 4—**Computerized Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

February 2-4—**Genitourinary Pathology—4th Annual Course.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 20 hrs. $150. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

February 19-20—**Computerized Scanning of Body and Head—10th Annual Leo G. Rigler Radiology Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday.

SURGERY AND ANESTHESIOLOGY

December 2-3—**Medical and Surgical Complications of Uveitis.** UCSF. Thursday-Friday.

December 3-4—**Intraocular Lens Implantation.** Santa Monica Hospital Medical Center, Santa Monica. Friday-Saturday. 16 hrs. $600. Contact: Jeanne Harris, Charlie Ruggles Ophthalmology Dept., Santa Monica Hosp. Med. Ctr., 1225 15th St., Santa Monica 90404. (213) 451-1511, ext. 2148.

December 3-5—**Electronystagmography Workshop.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

December 3-5—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Friday-Sunday. $300; $150 for residents.

December 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

December 9-11—**Trauma.** American College of Surgeons at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. $125. Contact: Frank R. Lewis, MD, Dept. of Surgery, San Francisco General Hospital, San Francisco 94110.

December 11—**Anesthesia Update: New Agents and Techniques.** Valley Anesthesia Society of Sacramento, UCD and Calif. Society of Anesthesiologists at Red Lion Inn, Sacramento. Saturday. Contact: John H. Eisele, MD, Dept. of Anesthesiology, UCD School of Medicine, Davis 95616.

January 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 14-15—**Surgical Symposium.** Santa Clara County Surgical Society and San Jose Surgical Society at LeBaron Hotel, San Jose. Friday-Saturday. 16 hrs. $125. Contact: Lawrence Stern, MD, 2505 Samaritan Dr., Suite 606, San Jose 95128, (408) 358-1801; or Joseph Brozda, MD, 25 N. 14th St., Suite 460, San Jose 95112, (408) 287-7434.

January 17-21—**Otologic Surgery Course—12th Annual.** Ear Research Institute, Los Angeles. Saturday-Wednesday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 22-23—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

January 23-27—**Midwinter Clinical Convention.** Research Study Club of Los Angeles at Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: Research Study Club of Los Angeles, Inc., Box 49412, Los Angeles 90049. (213) 879-0143.

January 26-28—**Advances in Neurology.** See Medicine, January 26-28.

January 28-30—**Pediatric Anesthesiology—15th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $125. Contact: Wayne Herbert, MD, Prog. Dir., CHLA, 4650 Sunset Blvd., Los Angeles 90054. (213) 660-2450, ext. 2262.

January 30-February 2—**Theodore Billroth Surgical Anatomy Course.** LLU. Sunday-Wednesday.

January 31-February 4—**Management of Trauma.** UCSD at Sheraton-Harbor Island, San Diego. Monday-Friday.

February 3-4—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 12-18—**Mid-Winter Nasal Symposium.** STAN at Harrah's, South Lake Tahoe. One week. $275; $175, residents. Contact: Willard E. Fee, Jr., MD, Division of Otolaryngology, Room 135, Stanford Univ. Medical Ctr., Stanford 94305. (415) 497-5828.

February 23-25—**Anterior Segment Disease in Surgery.** USC. 21 hrs. Wednesday-Friday.

February 23-27—**Controversial Areas in Surgery of the Head and Neck.** UCSD at Vacation Village Hotel, San Diego. Wednesday-Sunday. Contact: Alan M. Nahum, MD, 225 W. Dickinson St., San Diego 92103. (714) 294-5910.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

November 15-19—**Dermatology for Primary Care Physicians.** UCSF. Monday-Friday. $400. Intensive preceptorial course presenting practical management of skin diseases that constitute a large part of daily practice. Enrollment limited to 10 primary care providers.

November 29-December 3—**Advances in Diagnosis and Treatment in Clinical Medicine.** See Medicine, November 29-December 3.

December 1-3—**Immunizations—Review and Predictions.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

December 2-5—**Treatment of Sexual Dysfunctions.** USC at Canyon Hotel, Palm Springs. Thursday-Sunday.

December 9-11—**Genetics.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday.

December 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

January 10-14—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Sheraton-Harbor Island, San Diego. Monday-Friday.

January 10-June 27—**Medical Progress/Medical Practice.** UCSF. Mondays. 7:30-9:30 p.m.

January 13-14—**New and Old Antibiotics.** USC. Thursday-Friday.

January 18-21—**Diagnosis and Management of Seizure Disorders.** UCLA at Palm Springs. Tuesday-Friday.

January 22—**Gerontology.** John Muir Hospital and Walnut Creek Based Educational Committee at John Muir Hospital, Walnut Creek. Saturday. Contact: Marshall Y. Kremers, MD, 2528 Ptarmigan Dr., No. 3, Walnut Creek 94595. (415) 938-0568.

January 22-23—**Biofeedback and Meditation: Stress and Self-Regulatory Therapies.** UCSF and The Institute for the Study of Human Knowledge. Saturday-Sunday. 12 hrs. Contact: Ms. Mae Ling Yee, Cont. Ed. in Health Sciences, Room 135G, UCSF. (415) 666-2894.

January 22-February 27—**Basic Acupuncture.** PMC. Saturdays and Sundays. $1,100.

January 23-28—**Emergency Medicine.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sunday-Friday.

January 24-28—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

January 29—**Hypertension.** USC. Saturday.

January 31-February 5—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 1-5—**Physician and Hospital.** USC at Ahwahnee Hotel, Yosemite. Tuesday-Saturday.

February 6-11—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Sunday-Friday.

February 9-11—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Continuing Medical Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600.

February 9-11—**Conference on Winter Sports Medicine—2nd Annual.** CMA, Medical Foundation of Santa Barbara County and UCLA at Mammoth Mountain. Wednesday-Friday. Contact: CMA.

February 9-12—**Primary Care—Current Management of Common Office Problems.** UCSF. Wednesday-Saturday.

February 22-26—**Sports Medicine—Ski Injuries.** UCSF at Lake Tahoe. Tuesday-Saturday.

February 26—**Workshop for Physicians and Health Professionals.** UCLA. Saturday.

February 28-March 4—**Basic Science for Clinicians.** STAN. Monday-Friday. $250.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation —32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Stanford University School of Medicine

Office of Postgraduate Medical Education

announces a multidisciplinary course on

CANCER

JANUARY 24-28, 1977

at Stanford University

A five-day multidisciplinary symposium on "Cancer" will be presented for physicians and surgeons who deal with problems related to neoplastic disorders. Lectures, case presentations, and informal seminars will provide each registrant with an opportunity to assess his present knowledge and practice and to acquire new information and skills of clinical pertinence. General lectures will cover:

- Molecular Biology of Cancer
- Carcinogenesis
- Cell Cycles and Cytokinetics
- Ultrasound
- Scintigraphy
- Body Scanning—Computerized Axial Tomography
- Staging
- Principles of Radiation Therapy
- Principles of Chemotherapy
- Specific Chemotherapeutic Agents
- Adjuvant Chemotherapy
- Endocrine Therapy and Ablative Procedures
- Tumor Immunology
- Management of Infection
- Use of Blood Components
- Hodgkins and the Other Lymphomas
  - Diagnosis and Classification
  - Staging Procedures
  - Radiation Therapy and Chemotherapy
- Breast
  - Diagnosis and Staging
  - Surgery and Radiation Therapy
  - Medical Management

Concurrent sets of elective afternoon sessions will include:

- AML, ALL, CML, CLL, and Plasma Cell Neoplasms
- Head and Neck, Prostate, Thyroid
- Melanoma, Medical Management of GI Neoplasms and Bronchogenic Neoplasms
- Acute Leukemia in Children, Solid Tumors in Children, Rehabilitation of the Child and the Family

Faculty for the course will consist of 32 members of the Stanford University faculty.

The Postgraduate Medical Education Program of Stanford University School of Medicine is fully accredited by the AMA and CMA continuing education programs, with this course being acceptable for up to 27 hours of Category I credit.

Tuition: $250. Registration is required no later than January 21.

For registration, brochure or further information address:

Office of Postgraduate Medical Education
Room TA-145
Stanford University Medical Center
Stanford, California 94305
Phone (415) 497-5594

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

Providence Hospital, 700 N.E. 47th Avenue, Portland 97213:

November 24—Medical and Surgical Audit Review—8:00 a.m.

December 1—The Adult Respiratory Distress Syndrome—8:00 a.m.

December 8—Biofeedback in Medicine—8:00 a.m.

December 22—Staphylococcal Disease: Selected Aspects of Diagnosis and Treatment—8:00 a.m.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Dpartment of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland 97201.

February 14-18—**Family Practice Review.** Sheraton Hotel, Lloyd Center, Portland. Contact: William A. Fisher, MD, Department of Family Practice, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

November 14-16—**Lifestyle and Its Impact on the Health of Oregonians,** Valley River Inn, Eugene. Contact: Mrs. Alicia Swindel, Oregon Public Health Association, 426 S.W. Stark, Portland 97204.

December 1—**Clinical Use of Medications.** Thunderbird Inn at the Quay, Vancouver, WA. Contact: Jay S. Wakefield, MCSA, 215 University District Building, 1107 N.E. 45th, Seattle, WA 98105.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

November 17—**Allergy.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 293-3101.

November 18—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

November 19—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

November 19—**Treating the Untreatable.** Friday. Spokane. 4 hrs. Physicians, $25; others, $15. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

November 22—**Internal Medicine Review: Nuclear Medicine.** Monday. Univ. of Wash. in Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

November 23—**Internal Medicine Review: Nuclear Medicine.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

November 30—**Surgery: Shock and Clinical Fluid Balance.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Leonard W. Brewer, MD, 2833 Ft. Missoula Rd., Missoula, MT 59801. (406) 728-6815.

December 1—**Surgery: Shock and Clinical Fluid Balance.** Wednesday. Univ. of Wash. in Billings, Mont. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

December 10—**Psychiatry for the Non-Psychiatrist.** Friday Virginia Mason Medical Center Auditorium, Seattle. 7 hrs $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

)ecember 16—**Internal Medicine Review: Medical Genetics.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

)ecember 17—**Internal Medicine Review: Medical Genetics.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

)ecember 27—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

)ecember 28—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

ınuary 7—**Medicine and the Law I.** Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

ınuary 11-14—**Fluid and Electrolyte Balance.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. 8 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98410. (206) 756-3152.

ınuary 13-14—**Pediatrics.** Thursday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

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ınuary 24—**Internal Medicine Review: Hematology.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

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ınuary 27—**Internal Medicine Review: Immunologic Renal Disease.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext 258.

nuary 27—**Radiation-Oncology.** Thursday. 7:30-10:30 p.m., Tacoma General Hospital, Tacoma, Wash. 3 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

nuary 28—**Internal Medicine Review: Immunologic Renal D.sease.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

nuary 28—**What's New in Liver-Biliary Disease.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 6½ hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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ebruary 1—**Surgery: Chest Trauma and Diseases of the Lower Esophagus.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Leonard W. Brewer, MD, 2833 Ft. Missoula Rd., Missoula, MT 59801. (406) 728-6815.

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February 10-11—**Medical and Surgical Aspects of Urinary Tract Disease.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 13 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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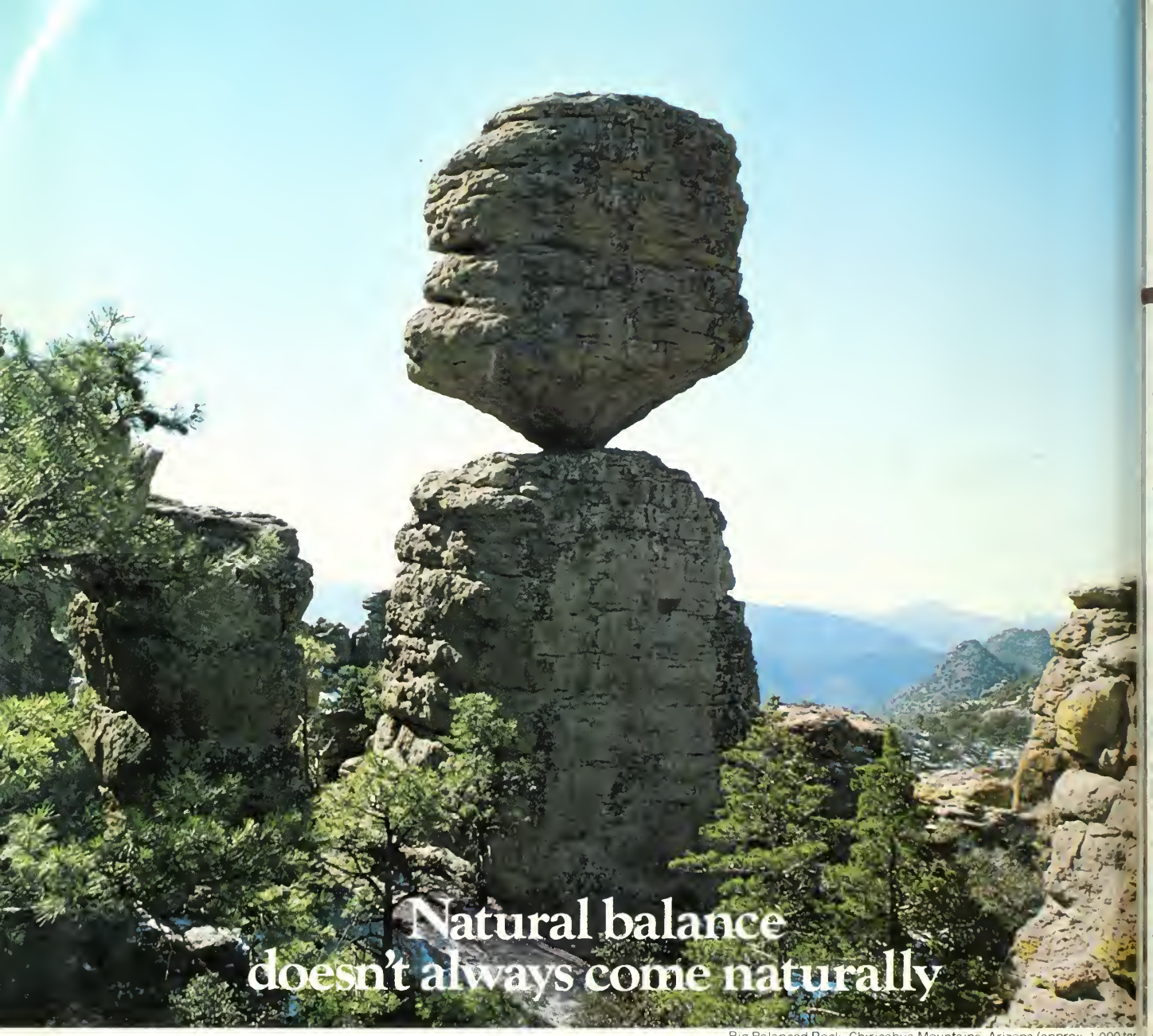
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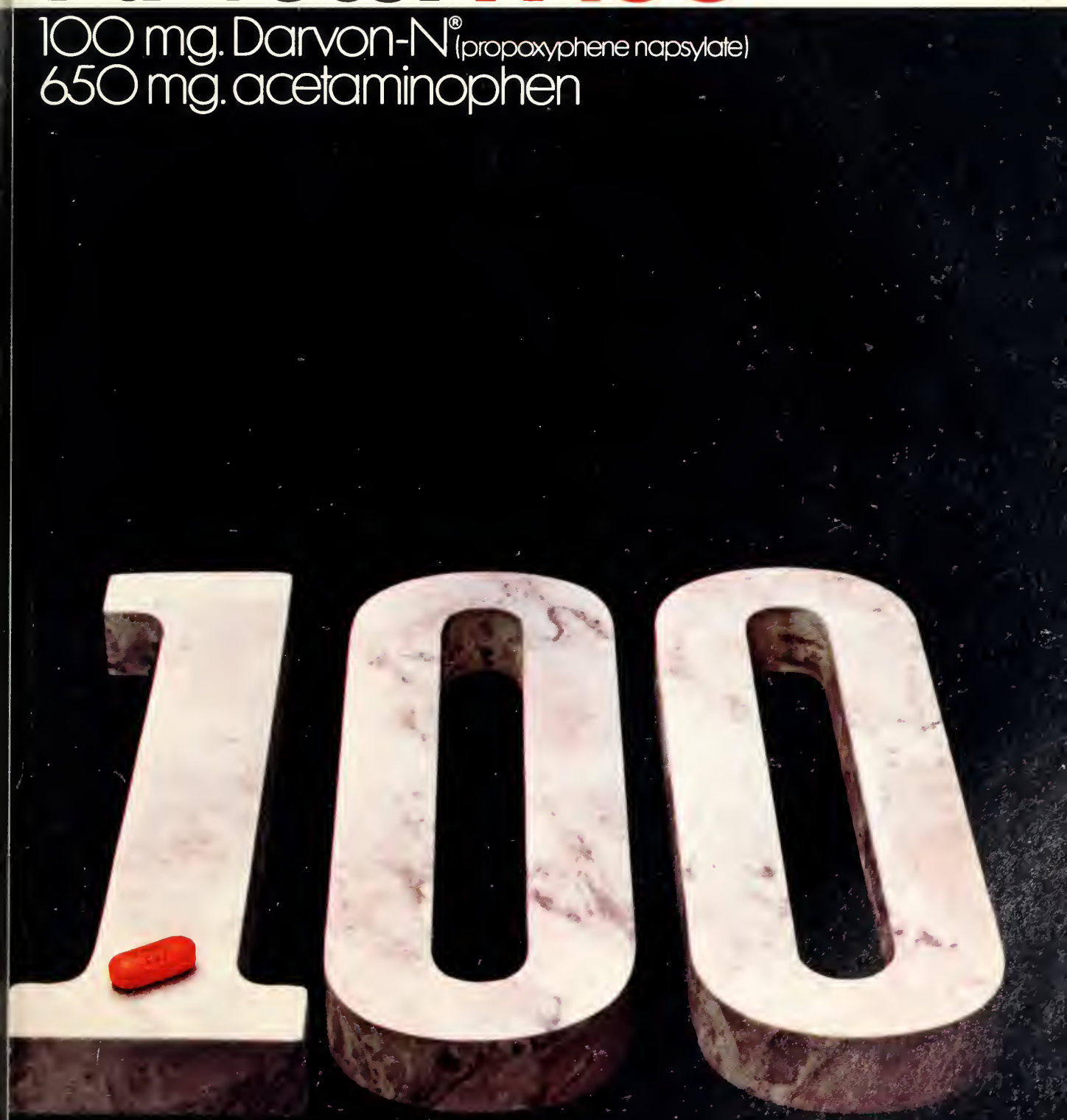

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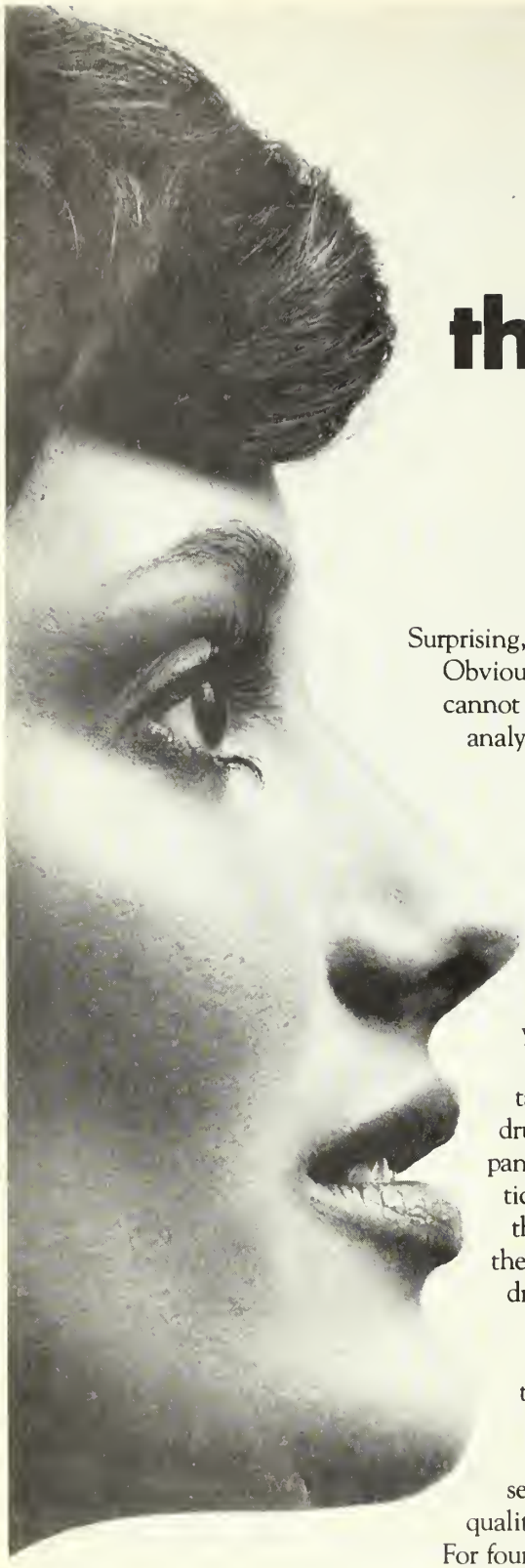

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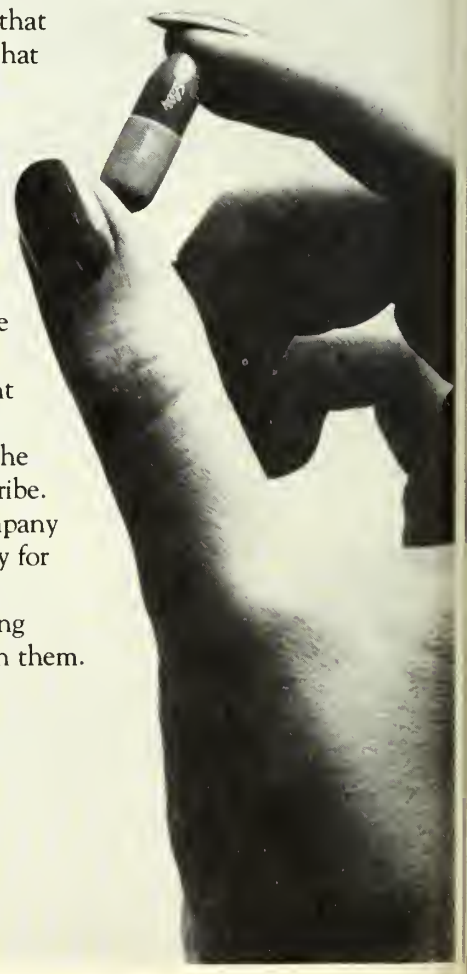

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THE WESTERN
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Gallium-67 Scintigraphy and Intraabdominal Sepsis

Clinical Experience in 140 Patients with Suspected Intraabdominal Abscess

G. BRUCE HOPKINS, MD; MICHAEL KAN, MD, *and* CHRISTIAN W. MENDE, MD
La Jolla, California

In 140 patients with suspected intraabdominal abscess, studies were made using gallium-67 citrate and technetium-99m labeled radiopharmaceuticals. Gallium-67 scintigrams correctly localized 52 of 56 intraabdominal abscesses confirmed at surgical operation or necropsy. In an additional 20 patients in whom findings on scintigrams were abnormal, there were clinically established infections. Sixty-one patients in whom findings on scintigrams were normal were conservatively managed and discharged from the hospital; none proved to have an abscess. Four false-negative and three false-positive studies were recorded. Gallium-67 scintigraphy is a useful noninvasive diagnostic adjunct that should be employed early in the evaluation of patients with suspected intraabdominal sepsis.

LOCALIZATION of intraabdominal abscesses can prove a difficult and frustrating problem. Frequently the clinical impression of an occult abscess is not supported by findings on routine diagnostic studies including chest and abdominal roentgenograms, intravenous urography, abdominal ultrasonography and conventional liver-spleen scintigraphy. In these instances exploratory surgical operation is undertaken only after an extended work-up to locate the abscess and exclude other illnesses. The result may be extended periods of morbidity, protracted hospital stays and one or more operative procedures.

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Submitted April 30, 1976.

Reprint requests to: G. Bruce Hopkins, MD, Pathology-Nuclear Medicine, Scripps Memorial Hospital, La Jolla, CA 92037.

Gallium-67 (^{67}Ga) localization in inflammatory lesions was initially recorded by Lavender and co-workers,[1] with subsequent clinical and experimental corroboration by other investigators.[2-5] The study reviews our experience with ^{67}Ga scintigraphy in a large group of patients with suspected intraabdominal abscess.

Methods and Material

Gallium-67 is a cyclotron produced radionuclide that decays by electron capture, has a physical half-life of 78 hours and produces gamma energies of 93, 184, 296 and 388 kilo electron volts (keV), which are suitable for imaging with either scintillation cameras or rectilinear scanners. The whole-body radiation dose is approximately 0.3 rads per millicurie which is well within ac-

TABLE 1.—*Primary Disease in 76 Patients with Confirmed Inflammatory Foci*

Primary Disease	*Number of Cases*	*Primary Disease*	*Number of Cases*
Diverticulitis	16	Trauma	5
Genitourinary tract	13	Malignancy	4
Regional enteritis	10	Ulcerative colitis	3
Appendicitis	8	Septicemia	2
Pancreatitis	8	Amebiasis	1
Peptic ulcer	6		

TABLE 2.—*Results of ^{67}Ga Scintigraphy in Patients with Confirmed Inflammatory Foci*

	Location			
	Abdomen	*Pelvis*	*Subphrenic Space*	*Retroperitoneum*
Confirmed by surgical operation or necropsy	16	8	18	10
Confirmed clinically	8	4	0	8
False-positive	2	0	1	0
False-negative	2	0	2	0

Figure 1.—Posterior 6-hour ^{67}Ga-^{99m}Tc subtraction scintigram (liver, spleen and lungs subtracted) showing bilateral subphrenic abscesses developing five weeks after a hemicolectomy for bowel cancer.

ceptable limits.[6] The ^{67}Ga for this study was supplied as a sterile and pyrogen-free citrate by New England Nuclear Corporation.

Technetium-99m (^{99m}Tc) decays with a six hour physical half-life emitting monoenergetic 140 keV gamma radiation. Technetium-99m sulfur colloid, ^{99m}Tc-human albumin microspheres and ^{99m}Tc-glucoheptonate were used as liver-spleen, lung and kidney imaging agents, respectively. These agents were prepared in the Nuclear Medicine Laboratory from commercially available kits (New England Nuclear Sulfur Colloid and Glucoheptonate kits, 3M Brand Human Albumin Microsphere kit).

All studies commenced four to six hours after the intravenous administration of 3 millicuries of ^{67}Ga-citrate. In many patients delayed scintigrams also were done at 24 and 48 hours postinjection. Since approximately 15 percent of an intravenous dose of ^{67}Ga is excreted via the intestine,[6] laxatives were administered before delayed studies in an attempt to reduce colonic activity. Appropriate liver-lung, liver-spleen or kidney scintigrams using 2 millicuries of ^{99m}Tc-sulfur colloid, 2 millicuries of ^{99m}Tc-human albumin microspheres, or 10 millicuries of ^{99m}Tc-glucoheptonate were obtained with the early ^{67}Ga study. Anterior, lateral and posterior images were obtained.

Both the Anger scintillation camera and rectilinear scanner were employed. The camera studies were done with either a Searle Radiographics Pho/Gamma III-HP, Nuclear Data Radicamera-60 or a General Electric Radicamera-II scintillation camera using the 184 and 296 keV photopeaks, a 20 percent window and a medium energy diverging collimator. The Nuclear Data camera was equipped with two pulse-height analyzer windows that provided the capability of counting both photopeaks simultaneously. Either the 184 or 296 keV photopeak was employed when using the General Electric or Searle Radiographics scintillation cameras. The 140 keV photopeak of ^{99m}Tc differs sufficiently from the photopeaks of ^{67}Ga so that combined studies using both radiopharmaceuticals are possible. The patient is maintained in the same position and single or double exposures, using window settings for ^{67}Ga and ^{99m}Tc respectively, are obtained on Polaroid film and magnetic tape. The scintillation cameras are interfaced to a Nuclear Data ND 812 computer.

Rectilinear studies were carried out with the 3-inch Searle Radiographics Pho/Dot scanner and the Raytheon 5-inch dual-probe whole body scanner. Range 1 (15-120 keV), 30 percent suppression and the 19-hole collimator were used with the Searle Radiographics scanner. When scanning with Raytheon electronic pulse-height analyzer subtraction, 30 percent contrast enhancement, 2:1 minification and medium-energy collimators were used. A 85-350 keV window was used when pulse-height analyzer subtraction was deemed unnecessary. Scan speed was adjusted to obtain a minimum information density of 600 counts per cu cm.

With electronic pulse-height analyzer subtrac-

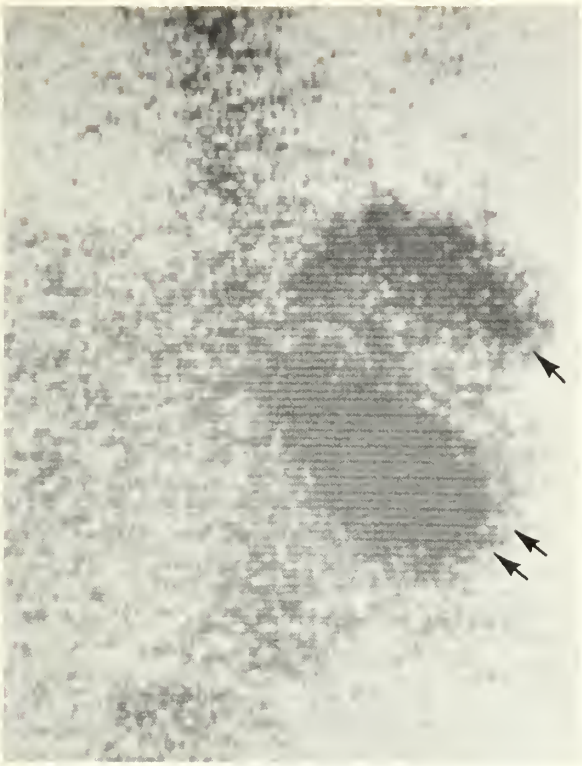

Figure 2.—Posterior 6-hour ^{67}Ga scintigram in a patient with pancreatitis **(double arrows)** and a left subphrenic abscess **(single arrow).**

Figure 3.—Anterior 4-hour ^{67}Ga scintigram showing a left subphrenic abscess, fistula tract and right upper quadrant abscess two weeks after a splenectomy and partial bowel resection for abdominal trauma.

Figure 4.—Posterior 6-hour ^{67}Ga-^{99m}Tc subtraction scintigram (kidneys subtracted) showing a perinephric abscess that developed two weeks after a colectomy for ulcerative colitis.

tion technique, all signal pulses corresponding to both ^{67}Ga and ^{99m}Tc gamma interactions from the anterior or posterior probe are directed to both pulse-height analyzers. One pulse-height analyzer, by way of energy selection, permits the 184 and 296 keV photopeaks of ^{67}Ga to be recorded. The second pulse-height analyzer is adjusted to accommodate the 140 keV photopeak of ^{99m}Tc. Each pulse-height analyzer is normalized to 100 percent over the appropriate area. Two scintiscans are produced simultaneously. One represents the distribution of ^{67}Ga while the other represents the distribution of ^{67}Ga minus the distribution of ^{99m}Tc.

Results

This series is comprised of 140 patients with suspected intraabdominal abscess referred to the Nuclear Medicine Laboratory during the interval from January 1973 to January 1976. All patients had fever; most had a variety of clinical and laboratory abnormalities suggestive of infection. In many instances the possible site of involvement

Figure 5.—Anterior 4-hour ^{67}Ga scintigram showing a chronic tubo-ovarian abscess in a patient with a fever of undetermined origin. Normal bladder activity is present below the abscess.

Figure 6.—Anterior 24-hour ^{67}Ga scintigram showing a deep pelvic paravaginal abscess that developed following pelvic trauma.

was either not evident or only suggested by routine diagnostic studies. In most patients signs of sepsis developed as complications of diseases, operations or injuries of the gastrointestinal or genitourinary tracts (Table 1).

The results of ^{67}Ga scintigraphy with respect to general location are summarized in Table 2. Patients with pyelonephritis were excluded from the group with retroperitoneal infections. Gallium-67 scintigrams correctly localized 52 of 56 deep abdominal abscesses confirmed by either surgical operation or necropsy. Examples are shown in Figures 1 through 7. An additional 20 patients with clinical evidence of deep abdominal infection and abnormal scintigrams were conservatively managed with antibiotics, which resulted in gradual defervescence and clinical improvement. In all likelihood, these latter cases represented ^{67}Ga localization in areas of diffuse inflammation rather than organized abscesses. In four of these patients repeat ^{67}Ga scintigrams carried out at intervals of three to six weeks showed resolution of the previous abnormality.

Sixty-one patients with fever and negative scintigrams were conservatively managed and discharged from the hospital. These studies had been obtained in patients with septicemia, in postoperative patients or in patients with predisposing gastrointestinal or genitourinary tract disease to rule out the possibility of an occult abscess. None of these patients proved to have an abscess.

Four patients with false-negative studies had surgically confirmed abscesses. The reason for the false-negative results is unclear though probably related to insufficient target-to-background ratios for abscess differentiation. Three false-positive studies were recorded. In retrospect, two of these represented errors in interpretation due to residual colonic activity. Although both had been negative on early scintigrams, they were subsequently judged abnormal on the basis of delayed studies. Purgatives had been contraindicated in both pa-

Figure 7.—Anterior 24-hour ^{67}Ga-^{99m}Tc subtraction scintigram (bladder subtracted) in a patient with diverticulitis and a peridiverticular abscess.

tients. The third false-positive study represented over-zealous interpretive error.

Discussion

Based on our experience, ^{67}Ga scintigraphy is warranted in patients with suspected intraabdominal abscess, particularly when other diagnostic modalities yield negative or equivocal results. Gallium-67 scintigrams not only localized 52 of 56 confirmed abscesses, but also proved instrumental in ruling-out infection in 61 patients originally thought to harbor occult infection. The low incidence of false-negative and false-positive results in this and other reported series[7,8] can be reassuring, particularly in postoperative patients in whom fever may develop for a variety of reasons. In addition, negative ^{67}Ga scintigrams in patients with evidence of sepsis strongly suggest that a localized focus is not present or that its size may be too small to be detected by other means.

The common practice in most laboratories is to delay ^{67}Ga scintigraphy for 24 to 72 hours after the intravenous injection to ensure optimal target-to-background ratios for abscess differentiation. Previous studies from this laboratory have shown this practice unwarranted due to the avidity of ^{67}Ga for inflammatory sites.[9,10] If early scintigrams are negative or questionable, delayed studies can then be obtained. To routinely delay ^{67}Ga scintigraphy in septic patients not only limits its clinical utility, but also contributes to prolonged patient morbidity.

Approximately 20 to 30 percent of an intravenous dose of ^{67}Ga-citrate is excreted by the kidneys,[6] with most of this occurring in the first 24 hours postinjection. After the first day the liver and biliary tract become the major route of excretion; therefore an additional advantage of early scintigraphy is the ability to image the abdomen without undue interference from colonic activity. Some bowel activity may be seen on early scintigrams though it is not nearly as pronounced as that present on 24 or 48 hour studies. When present, it is generally confined to the area of the cecum and right colon. Early scintigrams are particularly helpful in patients in whom cathartics are contraindicated.

The property of ^{67}Ga to localize in liver and spleen as well as in inflammatory foci can prove a problem in subphrenic abscess if target-to-background ratios are insufficient for abscess differentiation. This is of considerable import as the subphrenic space is the most common site of a postoperative abscess.[11] The combined study using ^{67}Ga-citrate and ^{99m}Tc-sulfur colloid is particularly helpful in this regard. The limits of the liver and spleen can be readily defined with ^{99m}Tc-sulfur colloid and the site of any abnormal ^{67}Ga localization outside these areas more accurately assessed. Combined studies using ^{99m}Tc-glucoheptonate to image the kidneys are helpful in cases of suspected perinephric abscess. In our experience, combined studies using the Raytheon rectilinear scanner with electronic pulse-height analyzer subtraction proved preferable to combined studies with the scintillation camera as it provided scintigrams that were easier to interpret.

The mechanism of ^{67}Ga localization in inflammatory foci has not been clearly elucidated. Suggested mechanisms include ^{67}Ga protein complexes accumulating about the inflammatory site[7] and the *in vivo* labeling of granulocytic leukocytes that migrate to the inflammatory focus.[12] A decrease in circulating granulocytes has correlated

with both a diminution in intensity and delay in onset of ^{67}Ga detection in experimental inflammation.[13]

In summary, ^{67}Ga scintigrams correctly localized 72 of 76 deep abdominal inflammatory foci. Gallium-67 scintigraphy is a useful noninvasive adjunct that should be employed early in the diagnostic work-up of a febrile patient with suspected intraabdominal sepsis.

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Correcting Inverted Nipples

I feel that there is a way that we can correct this abnormality [inverted nipples]. First, you instruct the girl to make an imaginary cross on her breast, using the nipple as the center part of the cross and making the arms of the cross at a 90-degree angle. In other words, there's a vertical line and a horizontal line meeting over the nipple. Then, she presses into the breast tissue adjacent to the areola and extends pressure laterally along the arms of the cross, first vertically and then horizontally (preferably done by the girl after a bath or a shower when the tissue is softer). She will find that over a period of time the inverted nipple will gradually become everted. Now after some eversion has occurred, it is important to grasp the partially everted nipple and pull it out further. If this is done repeatedly over a period of time, it does correct the inversion. . . . However, I must quickly add that even though the inversion has been corrected, I cannot guarantee that it would be satisfactory for breast feeding. However, I urge that this approach be tried.

—J. BROOKS HOFFMAN, MD, *Greenwich, CT*

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Varicocele and Infertility in Men

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Varicocele is an important cause of infertility in men. The exact mechanism by which varicocele depresses spermatogenesis is unknown but probably the retrograde flow of blood rich in catecholamines into the testes plays a major role.

Because subfertile semen qualities are present in a large percentage of men with varicocele and because the response to surgical procedures is very good, high ligation of the left internal spermatic vein is recommended in men with varicocele and infertility.

It is now generally accepted that varicocele can cause impairment in spermatogenesis and that ligation of the left internal spermatic vein results in pronounced improvement in semen quality. The results reported here confirm these facts.

Materials and Methods

Between July 1973 and June 1975, a total of 57 patients with varicocele were referred to the Urology Clinic at the American University Medical Center. In all 57 patients at least one semen analysis was made and in 49 out of 57 cases there were abnormal findings on a spermogram. A spermogram is considered abnormal if the count is less than 20 million sperms per ml, if the motility is less than 50 percent at two hours, if there are more than 50 percent abnormal forms or any combination of these three measures.

A breakdown of the cases is found in Table 1. Of the 57 patients, 37 were referred for infertility, spermograms were abnormal in all, and 20 were referred because of the presence of a varicocele, spermograms were abnormal in only 12 of these. A profile of all semen analyses done on all 57 patients is shown in Table 2.

Of the 49 patients with varicocele and abnormal spermograms, 39 were treated surgically. The operation consisted of transection and ligation of the transected ends of the left internal spermatic vein at the level of the internal inguinal ring through a left inguinal incision. There were no postoperative complications and the average length of hospital stay was 2.5 days. All patients were back to their normal activities within eight days.

Results

Of the patients, 37 were followed up for periods ranging from 5 to 14 months and 2 patients were lost to follow-up. Pronounced improvement in semen quality was noted in 27 of the 37 patients. A spermogram is considered improved when all three measures—count, motility and morphology—become within the normal range. Table 3 shows a profile of the semen analyses done on all 37 patients before and after ligation of the spermatic vein.

Table 4 breaks down the cases according to the preoperative sperm count. In all 37 patients there was low motility and a high percentage of abnor-

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mal forms whether the count was over or under 20 million sperms per ml. Of the 19 patients with counts over 20 million per ml, 18 improved; 8 of 12 patients with counts between 10 and 20 million per ml improved, and only 1 of 6 patients with counts less than 10 million per ml showed improvement postoperatively.

TABLE 1.—*A Breakdown of 57 Patients with Varicocele*

	Total Number of Cases	*Number of Cases with Abnormal Spermogram*
Patients with varicocele referred for infertility	37	37
Patients referred because of presence of varicocele	20	12
TOTAL	57	49

TABLE 2.—*Findings on Semen Analysis in the Presence of Varicocele*

	Patients with Varicocele and Normal Spermogram	*Patients with Varicocele and Abnormal Spermogram*
Number of patients	8	49
Number of semen analyses done	14	102
Volume of ejaculate (ml)	3.7	3.4
Sperm count (millions per ml)	62	16
Total count (millions)	229	54
Motility		
Actively motile	63%	41%
Sluggishly motile	31%	34%
Dead	6%	25%
Morphology		
Normal forms	72%	52%
Abnormal forms	28%	48%

TABLE 3.—*Findings on Semen Analysis of 37 Patients Before and After Ligation of Spermatic Vein.*

	Before	*After*
Volume of ejaculate (ml)	3.4	3.5
Sperm count (millions per ml)	18	42
Total count (millions)	61	147
Motility		
Actively motile	39%	59%
Sluggishly motile	37%	24%
Dead	24%	17%
Morphology		
Normal forms	53%	68%
Abnormal forms	47%	32%

TABLE 4.—*Results of Ligation of Spermatic Vein on Semen Quality in 37 Patients*

Sperm Count (millions/ml)	*Number of Patients*	*Number Improved*	*Percent Improved*
More than 20 million	19	18	95
Between 10 and 20 million	12	8	67
Less than 10 million	6	1	17
TOTAL	37	27	73

Discussion

In the past, men with varicocele were treated by suture ligating the pampiniform plexus of veins in the inguinal canal at two levels and tying the ligatures together. But surgeons often refused to operate on the basis that the condition is self-limiting, that the symptoms were trivial and were not relieved by the operation, and that the operation sometimes resulted in atrophy of the affected testis.[1] Since the investigation by Russell[2] between 1947 and 1954 and the report by Tulloch[3] in 1952 of the restoration of fertility in an azospermic man after varicocele ligation, fresh thinking has been devoted to this subject.

The pathogenesis of subfertility associated with varicocele is not known. A varicocele develops as a result of the absence or incompetence of the valves of the left internal spermatic vein, particularly the valve at the junction of the spermatic and left renal vein,[4,5] causing retrograde flow of blood from the renal vein down the spermatic vein into the pampiniform plexus and, through cross-collateral venous communications, to the opposite side.[4] Therefore, any factor affecting spermatogenesis of the left testis will affect the right testis as well.

Whether the insult to spermatogenesis brought about by the presence of varicocele is due to a disturbance in thermoregulation[6,7] or whether it is due to increased adrenal steroids[5] and catecholamines,[8] there is histologic evidence of bilateral spermatogenesis arrest[9] which is corrected by ligation of the left internal spermatic vein. Clinically, this is manifested by improvement in semen quality in a good number of men.[5,10-12] In this series the overall improvement was 73 percent.

Although the incidence of varicocele has never been accurately determined, it is generally believed that 10 percent of men between the ages of 20 and 40 years have varicoceles. How many of these will be infertile is not known. In this report, of the 20 men seen because of a varicocele discovered on routine physical examination, in 12 spermograms were abnormal, making the incidence of subfertile semen quality in men with varicocele 60 percent. Three of the remaining eight patients with varicocele and normal findings on analysis of semen were followed up for six months to one year and in one of the three patients semen quality dropped to below the normal

fertile levels, increasing the subfertility incidence to 65 percent.

From the study of this group of men with varicocele it seems reasonable to assume that varicocele is uniformly detrimental to spermatogenesis, and the fact that some men with varicocele are fertile should not minimize the potentially detrimental role of this abnormality.

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Equating Anxiety and Low Blood Sugar

I think what's going on in our "epidemic of hypoglycemia" is as follows: the prevalence of low glucose values is great; the prevalence of anxiety, neuroses and psychosomatic symptoms in our population is also very great. Many patients are desperately seeking an organic basis for their symptoms. There is a certain similarity in the symptoms of hypoglycemia and of anxiety. In anxiety there is an epinephrine discharge, in hypoglycemia there is an epinephrine discharge. So there is a sort of physiological reason to have this similar array of symptoms. And we have a situation in which a lot of anxiety is occurring and a lot of low blood glucose values are being seen; we are starting to equate the two. And in my view, that is not valid.

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Medical
PROGRESS

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Neurochemistry and Behavior in Man

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The distribution and functions of certain neurotransmitter substances seem to correlate with clinical, anatomical and physiological evidence about the mediation of normal and abnormal behaviors in man, though much remains to be learned. The biosynthetic and metabolic pathways, receptors and reuptake mechanisms, and relationships to cyclic nucleotides for several major neurotransmitters are characterized, as well as the specific actions of many behavior-modifying drugs employed clinically. Experimental systems, including nerve cells in culture, permit tests of molecular actions inferred from biochemical and neurophysiological analyses in intact brain. This selective review emphasizes advances in neurochemistry which provide a context for current and future research on neurological and psychiatric disorders encountered in clinical practice.

THE CELLULAR AND BIOCHEMICAL organization and functions of the brain are under intensive investigation in man, as well as other species. The neurosciences are expanding rapidly, reflected in multidisciplinary research groups and in a burgeoning literature of journal articles and books.[1-9] Much has been learned about the roles of specific neurotransmitter molecules in anatomically and pathologically defined pathways in the brain. Meanwhile, the widespread clinical use of behavior-modifying drugs having defined biochemical actions has provided observations and generated hypotheses that relate neurochemical findings to normal and abnormal behaviors in man.

This review will emphasize principles of the organization and function of the nervous system, including the roles of specific neurotransmitters and their receptors, the involvement of cyclic nucleotides, and the phenomenon of disinhibition. Recent advances in biochemistry of depression, schizophrenia and opiate addiction will be highlighted.

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Principles of Organization

Nerve Cells Are Extremely Heterogeneous

Nervous tissue has two special properties: first, its electrically excitable cells, neurons, can conduct bioelectric signals over long distances without any loss of signal strength; second, these cells form specific intercellular connections with other nerve cells, muscle and glands, directing a grand array of bodily functions. Neurons are highly heterogeneous in size and shape. Neurons may have just one process, as in sensory ganglia and dorsal root ganglia, or two processes, as in bipolar sen-

ABBREVIATIONS USED IN TEXT

ACh = gamma-aminobutyric acid
AChR = nicotinic receptor for ACh
AChE = acetylcholinesterase
AMP = adenosine monophosphate
ATP = adenosine triphosphate
ChA = choline acetylase
COMT = catechol-O-methyltransferase
DA = dopamine
DBH = dopamine-beta-hydroxylase
DNA = deoxyribonucleic acid
dopa = dihydroxyphenylalanine
5HT = 5-hydroxytryptamine (serotonin)
GABA = gamma-aminobutyric acid
GAD = glutamic acid decarboxylase
GMP = guanosine monophosphate
LSD = lysergic acid diethylamide
MAO = monoamine oxidase
NE = norepinephrine
RNA = ribonucleic acid
TH = tyrosine hydroxylase

sory receptor cells of the retina, olfactory mucosa, auditory nerve and small granule cells within the brain. Most neurons are multipolar, with an axon of variable length and branching and many dendrites constituting a receptive field for the nerve cell body. Axons and dendrites form specialized nontouching connections called synapses, where much of the neurochemical story takes place.

With regard to neurochemistry, the interior of the neuron may be described briefly as having a nucleus and nucleolus, where the deoxyribonucleic acid (DNA) genetic material is carried and transcribed into ribonucleic acid (RNA); polyribosomes in the cell body, for active protein synthesis; mitochondria throughout the cell to support energy metabolism; microfilaments and microtubules extending down the axon through which metabolites and proteins are rapidly or slowly transported to the axon terminal at the synapse, and a metabolically extremely active terminus in which neurotransmitter molecules are stored in synaptic vesicles from which these molecules are released into the synapse upon electrical stimulation.

The brain contains some 100 billion cells, 90 percent of which are two types of neuroglia: (1) fibrous astrocytes, found in close approximation to axons and dendrites and blood vessels, are thought to insulate conducting surfaces of neurons and affect spatial distribution of neuronal processes; (2) oligodendrocytes form concentric layers of their own surface membrane around an axon, generating the axonal myelin sheath. Even those axons that lack a myelin sheath have an enclosing single invagination of oligodendrocyte surface membrane. Although glia have been presumed to "nurture" the neurons and their processes and possibly even be involved in modulation of the bioelectric signal or the formation of memory traces, no such functions have been demonstrated and axons which are cut off from a cell body cannot survive on glial support.

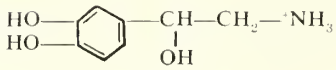
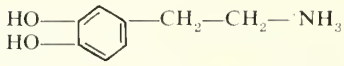
Finally, the vasculature of the brain and the blood-brain permeability barrier must be mentioned. The brain is extremely dependent upon oxidative metabolism and highly sensitive to lack of oxygen or glucose,[10] which are continuously distributed within the brain by the vascular system. The cerebral vasculature has a neurogenic mechanism to maintain blood flow even in the face of loss of volume or perfusion pressure elsewhere in the body.[11] The endothelial cells of brain capillaries differ from those in muscle and other tissues in having much more highly developed intercellular zones of membrane apposition without pinocytotic vesicles. Permeability barriers, when intact, protect the brain against blood-borne proteins and biological agents and also differentially admit lipophilic and keep out hydrophilic, charged small molecules, including many drugs and amino acid precursors. These barriers operate in both directions; thus, acid metabolites of monoamine neurotransmitters accumulate in the cerebrospinal fluid if probenecid is administered to block the acid transport system of the choroid plexus.

Neurons Make Connections Through Synapses: Neurotransmitters and Receptors

The synapse is a specialized contact zone between neuronal processes. The terminal portion of the axon is rich in microvesicles containing chemicals to be released as mediators of neurotransmission. Electron micrographs of the contact zone show dense material, presumably proteinaceous in nature, lining the intracellular portions of the presynaptic and postsynaptic membranes and filling the synaptic cleft between the apposed surfaces of the two cells. The material (neurostenin) consists of actomyosin-like proteins with Mg^{++}, Ca^{++}-activated adenosinetriphosphatase activity which may be involved in exocytosis, undergoing conformational changes with subsequent release of transmitter.[12]

The axon terminal is served by axoplasmic

TABLE 1.—*The Major Neurotransmitters*

Transmitter Molecule	*Formula*	*Precursor*	*Receptor Antagonist*	*Distribution*
acetylcholine (ACh)	$(CH_3)_3N^+—CH_2CH_2—O\overset{O}{\overset{\|\|}{C}}—CH_3$	choline	nicotinic d-tubocurare, α-bungarotoxin	neuromuscular junction, autonomic ganglia
			muscarinic atropine, QNB	brain, smooth muscle, glands
norepinephrine (NE)		tyrosine	β propranolol, α phentolamine	midbrain, hypothalamus, cerebellum
dopamine (DA) ...		tyrosine	phenothiazines, butyrophenones pimazide	substantia nigra, basal ganglia, limbic area
serotonin (5HT) ...		tryptophan	cyproheptadine, bromo-LSD	midbrain, raphe
gamma-aminobutyric acid (GABA)	$H_3N^+—CH_2CH_2CH_2—COO^-$	glutamic acid	bicucculine, picrotoxin	throughout brain (inhibitory)
glycine	$H_3N^+—CH_2COO^-$	glycine	strychnine	spinal cord (inhibitory)

QNB = 3-quinuclidinyl-benzilate

transport. Various organelles, enzymes and metabolites have been shown to flow from the cell body to the axon terminal at rates of from 0.1 to 400 mm per day, depending upon the type of tracer substance and the type of axon. Axon terminals have the necessary enzymes to synthesize neurotransmitter molecules from precursors present in the extracellular fluid spaces. Furthermore, several types of nerve terminals are capable of reaccumulating the released neurotransmitter from the synapse through an active reuptake process.

The elements of the synapse are the presynaptic axon termination, with its synaptic vesicles and packets of neurotransmitter and with its reuptake mechanism; the synaptic cleft itself, an intercellular space of 50 to 200 Angstrom units; and the postsynaptic receptor with high-affinity for a specific neurotransmitter. The biosynthetic and metabolic pathways for each transmitter are now well-established, and the enzymes for each step are becoming well characterized. Major advances have been made in the past few years in the identification and characterization of these receptors and in the design of receptor-blocking drugs with high specificity. Table 1 lists the six major transmitter molecules, their primary precursor and the agents used in studies of their receptors. These neurotransmitters, according to several lines of evidence, account for a minority of all the synapses in the brain. Thus, many other small molecules, including amino acids (aspartate, glutamate, taurine), histamine and peptides have been suggested as potential neurotransmitters. In invertebrates, and possibly in man, there are also electronic synapses, fused junctions which do not require chemical transmitters.

As a general rule, there is only one type of chemical neurotransmitter in the synaptic vesicles of any axon terminal. By contrast, neurotransmitters of many types may be released from their respective axons to act upon the dendritic branches of a single receptive neuron. These transmitters may act to excite or to inhibit the receptive cell, and the same neurotransmitter molecule may be excitatory on some cells and inhibitory on other cells.[3] Excitatory transmitters activate ionic conductance (permeability) of the postsynaptic membrane from the resting potassium equilibrium potential to the sodium equilibrium potential.[7,13,14] If depolarization is sufficient to reach the threshold for adjacent electrically excitable portions of the cell membrane, an all-or-none action potential will result. Inhibitory neurotransmitters appear to activate selectively conductance for chloride ion, hyperpolarizing the membrane. Slow postsynaptic potentials of several seconds' duration also have been described, accompanied by increased transmembrane ionic impedance (resistance), rather than conductance changes.

Many cell-cell connections in the brain occur over long distances, from a cell body in one region through its axon to the dendrites of a cell far removed, like the tracts of connections from substantia nigra to the striatum (basal ganglia).

These and many other tracts have been mapped by a remarkable technique pioneered by Falck and Hillarp[15,16] that identifies the axons containing biogenic amine neurotransmitters (norepinephrine, dopamine and serotonin). Each compound gives characteristic fluorescence outlining the tracts containing them, when freeze-dried tissue sections are treated with dry formaldehyde vapor.[17] More recently, immunofluorescent and immunoenzymatic methods have been employed with antibodies directed against biosynthetic enzymes for specific neutrotransmitters.

Specific Neurotransmitter Systems

Specific neurotransmitter substances have been characterized by distribution of the compound itself, activity and distribution of enzymes required for its synthesis and catabolism, presence of specific reuptake into nerve endings from different regions of brain, biochemical and behavioral effects of drugs that inhibit these enzymes or reuptake systems, distribution of receptors for the neurotransmitter, effects of the neurotransmitter when applied by microiontophoresis to the surface of receptor cells and, finally, the congruence of such biochemical observations with clinical-anatomical inferences about brain functions.

Many of the most important experiments were done first or only with systems other than brain. These experimental systems include the neuromuscular junction and the electric organ of the electric eel for acetyl choline; the adrenal medulla and sympathetic ganglia for catecholamines; the squid giant axon and *Aplysia* for ionic changes involved in bioelectric phenomena; and the large neurons of the crayfish for the inhibitory actions of gamma-aminobutyric acid (GABA) and excitatory actions of glutamate.

Acetylcholine (ACh)

This substance was recognized as a neurotransmitter in the 1920's. ACh is the primary transmitter at the neuromuscular junction, in autonomic ganglia, at postganglionic parasympathetic nerve endings, and for motoneuron collaterals to Renshaw cells in the central nervous system (Table 1). It is synthesized in one step from choline and acetyl coenzyme A (CoA) by the enzyme choline acetylase (ChA) in the nerve endings of cholinergic nerves. ACh is inactivated by hydrolysis by acetylcholinesterase (AChE). AChE has been characterized extensively from the electric organ and from brain; potent inhibitors are known, including organophosphorus compounds which are used as insecticides and nerve gases and readily reversible inhibitors, like physostigmine, which are utilized clinically. AChE is distributed widely throughout the brain, associated with synaptosomal, axonal and glial membranes; it is not a useful marker for cholinergic nerves. ACh itself has been extremely difficult to assay, so progress on the identification of cholinergic neurons in the brain has awaited the sensitive assay and immunohistochemical localization of ChA. ChA has highest activity in the caudate nucleus, retina, corneal epithelium and central spinal roots, with very low activity in dorsal spinal roots and cerebellum. No clinically useful inhibitor of ChA is available. The nicotinic receptor for ACh (AChR) has been isolated and characterized in much detail.[18,19] Some of its properties, especially the topography of binding sites for ACh, are very similar to those of AChE; however, experiments with snake venom α-bungarotoxin, which binds irreversibly to cholinergic receptors in neuromuscular junctions and in electric organ preparations, have distinguished AChR from AChE on postsynaptic membranes.

Cholinergic input involving entirely different muscarinic receptors has been demonstrated in the hippocampus, ascending reticular arousal system, caudate nucleus, parts of the thalamus and pyramidal cells of the cerebral cortex.[20] Sensory afferents from auditory, visual, taste, thermal and chemoreceptors also may be cholinergic. The important drugs affecting cholinergic systems in the brain are atropine and scopolamine, which produce a reduction in ACh content in the cerebral hemispheres. However, the amnesic effects are not well explained, since more potent ACh depleting drugs (hemicholinium) have no such behavioral effect. Certain peripherally acting organophosphorus anticholinesterases produce agitation, confusion and slowed intellectual and motor performance in psychological testing.[21] Again the mechanisms are still mysterious.

The most clearly elucidated pathology of cholinergic systems involves patients with myasthenia gravis. The disease appears to be mediated by antibodies directed against the nicotinic ACh receptor in neuromuscular junctions, causing deficiency of receptor sites and the characteristic syndrome of weakness.[22] Administration of anticholinesterase drugs, such as physostigmine, increases the duration of action of released ACh, overcoming the weakness. The similarity between

AChR of electric eels and of the human neuromuscular junction is sufficiently great that purified electric organ AChR has been employed to produce experimental autoimmune myasthenia gravis (EAM) in animals, including monkeys.[23] Lymphocytes from patients with myasthenia gravis have been transformed *in vitro* when cultured with the AChR, and lymphocytes from patients who improved clinically on prednisone gave notably diminished cellular responses.[24] Furthermore, a link to the peculiar relationship of the thymus to myasthenia gravis is provided by evidence that electric organ AChR cross-reacts on both humoral and cellular immune tests with components of calf thymus.[25]

Catecholamines: Norepinephrine (NE) and Dopamine (DA)

Norepinephrine is synthesized from the amino acid tyrosine by hydroxylation to dihydroxyphenylalanine (dopa), decarboxylation to dopamine, and then beta-hydroxylation to NE. Subsequent N-methylation, in adrenal medulla and in olfactory structures, produces epinephrine from NE.[26] NE is ubiquitous in tissues, serving as transmitter for adrenergic vasomotor fibers[11] in all tissues, except placenta and bone marrow, which lack such vasomotor innervation. In the 1940's von Euler identified NE in sympathetic ganglia and peripheral adrenergic nerves,[27] with the highest content of NE in the splenic nerve, almost exclusively containing nonmyelinated adrenergic fibers. NE was identified in mammalian brain, but for several years was thought to reflect only the vasomotor innervation; its concentration is highest in the hypothalamus.

NE-containing neurons in the brain[17] originate from cell bodies in the pons and medulla oblongata of the brain stem; ascending pathways make monosynaptic connections with cortical areas, limbic system (hippocampus, septum and related areas of the "emotional part" of the brain), and hypothalamus; descending pathways make connections with all parts of the spinal cord. The group of neurons most extensively investigated originates in the locus coeruleus and innervates the cerebellar and cerebral cortex and hippocampus. The cells in the locus coeruleus are densely packed and may all be noradrenergic, making electrophysiological recordings and selective stimulation or destruction quite feasible in experimental animals. The terminal networks of this system are very diffuse, with more than 100,000 terminals from an individual monoamine-containing cell body. These diffuse networks are thought to modulate complex phenomena underlying emotional mood, state of alertness, sleep, temperature regulation and neuroendocrine functions.[3,8,28] These central noradrenergic neurons are probably the primary site of action of antianxiety drugs such as benzodiazepines.[3]

Dopamine (DA) is not simply a precursor of NE. Its distribution differs notably from that of NE and it represents more than 50 percent of the total catecholamine content of the brain. The highest concentrations are found in the neostriatum (caudate and putamen of the basal ganglia), nucleus accumbens and olfactory tubercle. Its abundance in the basal ganglia has been related to extrapyramidal motor functions. There are three well-defined dopamine systems:[16,17] (1) nigrostriatal cell bodies are located in the zona compacta of the substantia nigra (the region that degenerates in Parkinson's disease) and project primarily to the neostriatum and the central amygdaloid nucleus; (2) mesolimbic dopaminergic cell bodies are located just dorsal to the interpeduncular nucleus in the ventral tegmental area and innervate the nucleus accumbens and olfactory tubercles (this system may be involved in emotional reactions); (3) tubero-infundibular dopaminergic cell bodies are found in the arcuate nucleus of the hypothalamus and innervate the external layer of the median eminence, stimulating release of luteinizing hormone releasing factor and growth hormone and inhibiting release of prolactin. With the precise localization of DA-containing neurons, it has been feasible to record the activity of these cells with extracellular single-unit techniques;[29] drugs that block the postsynaptic DA receptors (haloperidol, chlorpromazine) cause an increase in firing rate via a negative neuronal feedback loop from cells receiving DA input back to the cell body or dendrites of the DA-containing neurons, as proposed much earlier.[30]

The rate-limiting step in catecholamine biosynthesis is tyrosine hydroxylase (TH), a unique constituent of catecholamine-containing neurons and chromaffin cells. This enzyme disappears completely from renal, salivary gland, vas deferens and cardiac tissue upon chronic denervation of sympathetic nerves. The enzyme is stereospecific for L-tyrosine, requires molecular oxygen, Fe^{++}, and a tetrahydropteridine (folate) cofactor, and is associated with the synaptosome fraction from nerve endings. Inhibitors of TH, such as alpha-

methyl-p-tyrosine, reduce the nerve content of DA and NE and have been used to demonstrate the role of NE in exercise and stress and to treat patients with pheochromocytoma. The second step is mediated by L-aromatic amino acid decarboxylase, which acts on dopa and many other compounds and requires pyridoxal phosphate as cofactor. It is not restricted to neural tissues. Finally, the dopamine-beta-hydroxylase (DBH) is a copper-containing protein requiring molecular oxygen and ascorbate and localized to the membranes of amine storage granules in the nerve endings. Since this enzyme acts on certain related compounds, these substrates can replace NE at noradrenergic nerve endings and function as "false transmitters." One of the compounds that inhibit DBH is disulfiram, upon conversion to the copper chelating agent diethyldithiocarbamate. DBH has been difficult to assay in tissues, because of the presence of endogenous high molecular weight inhibitors. However, the enzyme has been purified from adrenal tissue and used to elicit specific anti-DBH antiserum. Furthermore, the release of NE from nerve endings is accompanied by a stoichiometric release of DBH,[31] so that DBH is found in the plasma and has been studied intensively, though inconclusively, as a marker for sympathetic nervous system activity.[32] The opportunity to assay a key enzyme in the peripheral circulation makes many experiments feasible, but the level of DBH activity seems to be more influenced by genetic factors than by any phenomena related to rate of firing of noradrenergic nerves.

Regulation of this pathway clearly occurs at the TH step, coupling the rate of DA or NE release or postsynaptic action, or both, to the need for additional synthesis.[28] Feedback inhibition by catecholamine products occurs, but other mechanisms of altering the rate of synthesis of the enzyme or its specific activity are probably involved, as well. Circulating hormones, including corticosteroids, thyroid hormones and angiotensin II, can influence NE synthesis.

An important advance in the understanding of catecholamines was the recognition that most of the NE in tissues is located within highly specialized granules in sympathetic and noradrenergic nerve endings and chromaffin cells. The granules contain adenosine triphosphate (ATP) in a molar ratio of NE/ATP = 4/1, presumably bound through salt linkages, DBH, Mg^{++}, Ca^{++}-dependent adenosinetriphosphatase, and a soluble protein chromogranin thought to be involved in the storage process. The amine storage granule protects DA and NE from degradation by monoamine oxidase (MAO), buffers their high ionic concentration, converts DA to NE in noradrenergic endings and serves as a depot for neurotransmitter release upon stimulation. The vesicles are formed in the neuronal cell body and transported to the nerve terminal region; if the axon is ligated or crushed, amine-containing granules can be shown to accumulate progressively on the proximal side of the ligation.[33] The antihypertensive agent reserpine depletes biogenic amines by irreversibly damaging these storage granules.

Metabolism of DA and NE is considerably slower than that for ACh and is mediated by MAO and catechol-O-methyltransferase (COMT). MAO oxidatively deaminates DA and NE to aldehydes, which are then oxidized to the corresponding acids. In the brain, NE is preferentially converted to the corresponding glycol-alcohol; ordinarily, COMT adds a 3-methoxy group to these compounds either before or after MAO oxidation. MAO acts intraneuronally, especially on DA, NE, or serotonin that "leaks" out of the granules; COMT acts within the synaptic cleft. Measurement of DA or NE or their metabolites in urine has provided nothing but controversial results in studies of brain function; at least 90 percent of NE metabolites come from the peripheral sympathetic nervous system and adrenal medulla. Even with measurements in the cerebrospinal fluid, results have been difficult to interpret, presumably due to the variety of dopaminergic and noradrenergic neuronal systems. Quantitatively and clinically, the most important process for terminating the action of DA and NE at synapses is reuptake into the presynaptic nerve ending.[34] Drugs that block reuptake include the tricyclic antidepressants, cocaine and amphetamines. Secondary amine derivatives such as desimipramine have enhanced potency against NE and little inhibition of DA uptake. Specific uptake of 6-hydroxydopamine, a cytotoxic compound, into dopaminergic and, to a lesser extent, noradrenergic neurons has provided a powerful experimental tool for "chemical sympathectomy" in the periphery and in the brain.[35] Studies with 6-hydroxydopamine permit localization by chemical lesions and assessment of behavioral consequences of destruction of DA and NE neurons.

In the past few years, it has been discovered that each of these processes may be investigated

in the peripheral blood. Mitochondrial MAO activity in platelets has at least certain properties in common with monoamine oxidase(s) of brain; COMT activity can be assayed in erythrocytes; and uptake of biogenic amines, particularly serotonin, into platelets mimics reuptake in the brain and is inhibited by similar drugs. In every case, much more detailed analysis is required to prove that the process in these peripheral sites is mediated by enzymes and membrane protein systems determined by the same gene as in brain and functioning in the same manner.

Entirely different classes of compounds block NE and DA receptors. The peripheral NE receptors which mediate cardiopulmonary responses are very well characterized pharmacologically, but not isolated biochemically. Blockers of alpha receptors (phentolamine, phenoxybenzamine) prevent hypertensive responses; blockers of beta receptors (propranolol) prevent increase in heart rate (beta-1) and bronchodilatation (beta-2). New agents which are extremely potent inhibitors of NE binding have been developed recently and tested both *in vivo* and on cultured cell lines *in vitro*. DA receptors are blocked by phenothiazines and butyrophenones, which act as antipsychotic agents, and are stimulated by apomorphine, a potent emetic.

The picture of DA neurons has been complicated by recent evidence strongly pointing to dendritic release of DA onto receptors on the same neuron, thereby inhibiting the firing rate of the neuron.[29,36] Amphetamines and other drugs affect the release and binding.

Serotonin (5-hydroxytryptamine, 5HT)

Since the mid-19th century, serum of clotted blood has been known to contain a substance which caused powerful constriction of smooth muscle organs, hence "serotonin." When the structure was elucidated, the indole ring resembled the structure of the psychedelic drug lysergic acid diethylamide (LSD), which also affected smooth muscle preparations. This relationship led to early theories that serotonin (5HT) in the brain might be involved in mental illness.[37]

5-hydroxytryptamine is synthesized in two steps from tryptophan, in a pathway highly analogous to catecholamine biosynthesis. The rate-limiting step is tryptophan hydroxylase, which requires molecular oxygen, tetrahydrobiopterin and sulfhydryl stabilizing compounds. The activity is sensitive to concentration of substrate, and active transport of tryptophan into the cells is significantly affected by dietary intake and diurnal variation in the plasma concentration.[38] Tryptophan hydroxylase is inhibited by p-chlorophenylalanine, which has been used to treat patients with carcinoid tumors. Subsequent decarboxylation of 5-hydroxytryptophan is mediated by the same L-aromatic amino acid decarboxylase which acts upon L-dopa. Catabolism of 5HT by MAO and reuptake of released 5HT into the presynaptic terminals are analogous to the steps in catecholamine systems. It should be noted that no more than 1 to 2 percent of the total body 5HT is found in the brain; about 90 percent occurs in the enterochromaffin cells of the gastrointestinal tract and 8 to 10 percent in the blood platelets. In rats and mice, but not man, additional serotonin is present in mast cells.

Despite the long history, much remains to be learned about serotonin, including regulation of its biosynthesis, characterization of its reuptake and receptors, description of its behavioral effects and actions of certain drugs. Other indoleamines may be present, as well. The pineal gland, situated outside the blood-brain barrier near the dorsal thalamus, contains high concentrations of 5HT, 50 times that of the whole brain. The metabolic activity of the enzymes related to 5HT synthesis and further conversion to melatonin (5-methoxy-N-acetyl-tryptamine) can be controlled by various external factors, including the neural activity of the sympathetic nervous system (NE) which innervates the pineal gland from the superior cervical ganglion. Cycles of environmental light and darkness determine a diurnal rhythm of both 5HT and melatonin.

Several methods have shown that almost all the serotonin-containing cell bodies in the central nervous system are restricted to a narrow group of neurons, known as the raphe nuclei, in the midportion of the lower pons and upper brain stem. Evidence was derived from classical neuroanatomical studies of the sites of degenerating axons after lesions in the medial forebrain bundle of the hypothalamus; by chemical assays for serotonin after such lesions, and by Falck-Hillarp fluorescence histochemistry after lesions and after loading animals with dietary L-tryptophan. When 5HT is administered by microelectrophoresis onto the surface of potential receptor cells, most respond by decreasing their firing rate.[39] Activation occurs in some limbic areas, but this effect could

be due to inhibition of adjacent inhibitory interneurons.

5HT is involved in temperature regulation, in perception or reaction to sensory stimuli, including pain, and in regulation of the sleep cycle. Electrical stimulation of the raphe nuclei in animals elevates body temperature and interferes with habituation to noise or repetitive sensory stimuli (a la LSD effect). Increase in brain 5HT with MAO inhibitors or intraventricular injection of 5HT or its precursor leads to increased time in slow-wave sleep; diminution in 5HT by ablation of the raphe nuclei or inhibition of 5HT synthesis with p-chloro-phenylalanine has the reverse effect producing insomnia. Several other neurotransmitter systems, especially NE from the locus coeruleus, have been implicated in the regulation of these sleep patterns.[40]

Gamma-Aminobutyric Acid (GABA)

GABA was identified in 1950 as a normal constituent of the mammalian central nervous system. No other tissue, except the retina, had more than a trace of GABA. Generalizing from the demonstrated role of GABA as an inhibitory neutrotransmitter,[41,42] Roberts has hypothesized that neuronal systems controlling behavioral sequences are held in check by inhibitory circuits, many utilizing GABA as neurotransmitter, and that inhibition may be released at appropriate moments either by overriding stimulation or by inhibition of the inhibitory neuron ("disinhibition"). However, much more needs to be learned about the integration of various circuits in specific regions of the brain.

GABA is synthesized from one of several pools of the metabolite glutamic acid in brain by decarboxylation;[43] glutamic acid decarboxylase (GAD) is the rate-limiting step in its formation. Metabolism of GABA involves transamination and oxidation, successively, by GABA-transaminase (GABA-T) and succinic semi-aldehyde dehydrogenase, to succinic acid. The transaminase regenerates alpha-keto-glutarate to provide a "glutamate shunt" without further involvement of the Krebs cycle. The highest concentrations of GABA occur in substantia nigra, globus pallidus, hypothalamus, the inferior and superior colliculi and the dentate nucleus (monkey data),[44] but GABA is present in substantial concentrations throughout the gray matter. Localization of GAD by immunofluorescence has confirmed these findings.[42] Both GAD and GABA-transaminase are dependent on the coenzyme pyridoxal phosphate. Deficiency or pharmacological inactivation of this cofactor can produce epileptiform seizures, associated with a reduction in GABA levels.[45] Rare B6-responsive seizures in childhood may be mediated, at least in part, by this mechanism.

GABA may undergo metabolic transformations to other compounds with functional activity in the brain. Gamma-hydroxybutyrate, formed by reduction of succinic semialdehyde, has anesthetic properties and specifically blocks impulse flow in dopaminergic neurons without any effect on NE, 5HT, or GABA neurons.[46] γ-amino-β-hydroxybutyric acid (GABOB), γ-aminobutyrylcholine, γ-butyrobetaine, γ-guanidinobutyric acid have depressant or excitatory effects on at least some neural systems, and γ-aminobutyrylhistidine (homocarnosine) is one of several dipeptides with significant concentrations in brain but unknown function.

There is no doubt that GABA serves as a potent inhibitory transmitter in the lobster nerve-muscle preparation and in the crayfish stretch receptor.[47] GABA release is proportional to the frequency of stimulation of the inhibitory axons and is blocked by lowered Ca^{++} concentration, which blocks neuromuscular transmission; GABA is present in 100 times higher concentration in inhibitory axons than excitatory axons; the enzymes, a specific GABA uptake mechanism, and GABA receptors, blocked by bicuculline and picrotoxin, all have been demonstrated. In mammalian systems, no such clear-cut evidence for roles of GABA has been gathered.[3,40,45] Compared with the other neurotransmitter systems, GABA lacks specific inhibitors of synthesis, uptake and receptor action and lacks well-defined, readily recorded clusters of GABA-containing neurons. One particularly promising system, however, involves the Purkinje cell axons from the cerebellum, which project onto cerebellar subcortical nuclei adjacent to the fourth ventricle (Deiter's neurons). Cerebellar stimulation increases the amount of GABA released into the ventricular perfusate, and GABA applied iontophoretically to Deiter's neurons induces inhibitory postsynaptic potential changes. Quantitative studies of GABA may be facilitated by the recent development of a radioreceptor assay using synaptosomal membrane fragments and the displacement of ^{3}H-GABA;[48] in fact, this type of assay may be useful for many other neurotransmitters.

Glycine

The simple amino acid glycine is metabolically related to glutamate, serine, folate and glyoxylate pathways and serves as an inhibitory transmitter in the inhibitory interneurons of the spinal cord ventral horn.[49] Iontophoretic application of amino acids in spinal cord preparations suggested that GABA and glycine were inhibitory, hyperpolarizing motoneurons and inducing permeability changes similar to those associated with postsynaptic inhibition. Anoxia of the lumbosacral cord produced by clamping the thoracic aorta destroys the interneurons preferentially, leaving motor neurons intact; analyses in these experiments showed significant decrease of glycine, but not of GABA. Stimulation of dorsal roots causes release of glycine from perfused spinal cord. Finally, strychnine, which blocks postsynaptic inhibition, blocks the action of glycine at presumed receptors.[50] Since chloride and other anions inhibit binding of strychnine to glycine receptors, it is likely that chloride is the ion whose conductance is increased by inhibitory synaptic action of glycine. As in the case of GABA, there are no well-defined neuronal pathways which can be isolated for detailed analysis of the role of glycine.

However, there is highly suggestive evidence that the benzodiazepines, including the two most commonly prescribed drugs in America, diazepam (Valium®) and chlordiazepoxide (Librium®), partly exert their antianxiety, anticonvulsant and muscle-relaxant effects by enhancing polysynaptic inhibitory processes at glycine receptors in the spinal cord, brain stem and thalamus.[51] The rank order of potency for 21 benzodiazepines in displacing ^{3}H-strychnine binding correlated with the rank order of potency in a variety of pharmacological and behavioral tests that predict clinical efficacy. No such correlation could be found for the weaker binding to opiate and cholinergic receptors, though additional sites of action for these drugs were not ruled out. Tetanus toxin also affects spinal cord inhibitory synapses involving glycine, by acting on presynaptic sites; the toxin (tetanospasmin) is transported from peripheral lesions by retrograde intraaxonal transport through motor neurons and across a synapse to the inhibitory nerve terminals.[52]

Other Potential Neurotransmitters

The majority of synapses remains unaccounted for even when all of the techniques presented above are employed to identify synapses utilizing each of the six major neurotransmitters. Certain amino acids occur in uniquely high concentrations in the brain and may serve neurotransmitter roles, as well. Glutamate and aspartate, the dicarboxylic amino acids, have strong excitatory effects in crustacean and mammalian spinal cord tests. Specific antagonists are required to evaluate the role of these compounds at synapses. The biggest problem about these compounds is their ready transformation into related metabolites. Certain complex amino acids, including taurine[54] and cystathionine, occur in unusually high concentrations in mammalian and primate brain; these two might be inhibitory transmitters. Finally, histamine,[55] formed from the amino acid histidine by specific decarboxylation, has some properties suggestive of a neurotransmitter role, including specific uptake into synaptosomes and differential regional concentration, highest in hypothalamus, intermediate in midbrain, and low in cortex and white matter (like the biogenic amines NE and 5HT). A functional role has not yet been delineated.

Neuromodulators: Cyclic AMP, Cyclic GMP, Prostaglandins, Peptides

In addition to the neurotransmitter substances which are released transsynaptically to effect rapid changes in ionic permeability and depolarize or hyperpolarize the postsynaptic membrane, there are other substances whose effects are longer-lasting and seem to modulate the firing rates of postsynaptic cells. It is likely that the two classes of substances are tightly interrelated.

Cyclic AMP

Brain contains extremely high activities of both adenyl cyclase and phosphodiesterase, the enzymes which synthesize and cleave cyclic adenosine monophosphate (AMP). In other tissues, of course, cyclic AMP has proved to be the intracellular mediator of the effects of epinephrine and most polypeptide hormones. In brain, norepinephrine, dopamine and probably serotonin all act by stimulating adenyl cyclase and increasing cyclic AMP concentrations in postsynaptic cells.[56] The adenyl cyclase appears to be intimately associated with the neurotransmitter-specific receptor. Cerebellar Purkinje cells have beta-adrenergic receptors; intracellular recordings reveal that NE hyperpolarizes these membranes, increases membrane resistance, and increases

cyclic AMP.[57,58] Iontophoretically applied cyclic AMP has the same effects, and inhibitors of the phosphodiesterase potentiate the effects of both NE and cyclic AMP. Dopamine-sensitive adenyl cyclases[59] have been demonstrated in rat caudate nucleus and in rabbit sympathetic ganglia. Serotonin increases cyclic AMP levels in rabbit brain slices[60] and, at least in insect neural tissue, stimulates adenyl cyclase activity; blockers of serotonin receptors (bromo-LSD and cyproheptadine) inhibit serotonin stimulation of cyclase activity.[61]

Greengard[56] has proposed a general scheme for amplification of the postsynaptic response by a cascade of reactions mediated by cyclic AMP-dependent phosphorylation of protein kinases; reversible phosphorylation of a membrane protein reversibly alters membrane permeability. The process is reversed by phosphoprotein phosphatases and by phosphodiesterase(s). Such tightly-coupled enzymatic events provide a means to integrate the inhibitory and excitatory influences of multiple synaptic inputs on a given cell. Cyclic AMP may be important also in other intracellular events, including synthesis of RNA and proteins, with long-term trophic effects.

Cyclic GMP

In many systems, there appears to be a balance of action between cyclic guanosine monophosphate (GMP) and cyclic AMP.[56] There is now good evidence in brain that acetyl choline stimulation of muscarinic receptors is mediated intracellularly by increase in cyclic GMP through increased guanyl cyclase activity, opening membrane channels for sodium-potassium exchange. Atropine, the classic muscarinic AChR blocker, prevents the increase in cyclic GMP.

Prostaglandins

The many compounds classified as prostaglandins fall into two series, the E series (extracted into ether) and the F series (extracted by fosphate).[62] In the sympathetic nervous system, prostaglandins of the E series affect both the release of transmitter from adrenergic terminals and the responsiveness of postsynaptic cells to NE. In the mammalian central nervous system, prostaglandins of the F series predominate over E series compounds. The distribution is rather uniform throughout the brain, not suggesting any association with specific pathways. Stimulation of the reticular formation causes release of prostaglandins from the cerebellar cortex, which can be blocked by pretreatment with chlorpromazine. Such stimulant compounds as picrotoxin, pentylene tetrazole and strychnine also release prostaglandins. Prostaglandins may act primarily through interaction with adenyl cyclase.

Substance P

When von Euler and Gaddum were assaying ACh in extracts from brain and intestine in 1931, they detected another pharmacologically active substance which was named substance P (isolated as a powder). This small peptide (ArgProLysProGluGlnPhePheGlyLeuMet-NH_2) is a potent vasodilator and constrictor of smooth muscle, found almost exclusively in the digestive tract and the nervous system.[63] In spinal dorsal root ganglion fibers, which are rich in substance P, this compound has an excitatory action with slow onset and relatively long duration. Substance P is found in high concentration also in the substantia nigra and midbrain structures. The synthetic peptide and antisera against this substance are being tested extensively, as are other peptides isolated from brain. Of these, the most interesting at present are two pentapeptides called enkephalins, which act as agonists at opiate receptors (see below).

Brain-Specific Proteins

In addition to enzymes involved in the biosynthesis and metabolism of neurotransmitter substances and receptors for their action, many other aspects of brain biochemistry have been examined. Most metabolic processes, including DNA, RNA and protein synthesis, much of intermediary metabolism, and the structural proteins in microtubules and microfilaments share the biochemical features of other tissues. It is of special interest, however, that the diversity of RNA messages, determined by hybridization to radioactively-labeled tracer sequences of single-copy DNA, is much greater in brain, especially cerebral cortex, than in other complex organs. This difference is greatest in man[64] and may reflect the complexity of higher cortical functions. The brain also has very active lipid biosynthesis and turnover, especially of phospholipids. Extensive studies of myelin composition and structure have been done, with importance for understanding the degenerative changes in multiple sclerosis and leukodystrophies.[1,2] Glia are especially rich in cortisol-inducible glycerol-3-phosphate dehydro-

genase for lipid synthesis. Figure 1 shows some of the multiple interrelationships among the neurotransmitter compounds and intermediary metabolites and certain substances having unusually high concentration in brain; these include GABA, taurine, cystathionine and N-acetylaspartate.

Two proteins have drawn a large portion of the investigation into special aspects of brain biochemistry. These are the S100 protein,[65] named for its solubility in 100 percent ammonium sulfate, and the 14-3-2 protein,[66] named for its positions on successive elutions from chromatographic columns. Antibodies have been prepared against each protein, assisting in the localization of S100 to glial cells and 14-3-2 to neurons.[67-69] These proteins are not species-specific. A protein termed antigen α is probably the same as 14-3-2.[70]

S100 and 14-3-2 have been useful markers for glial and neuronal cells in methods for bulk separation of these cell types and in characterization of cultured nerve cells *in vitro*. Mouse and human neuroblastoma cell lines and rat glial lines have been employed widely now in analyses of the processes of differentiation of such isolated cells, the appearance and regulation of neurotransmitters and their enzymes and receptors, and the in-

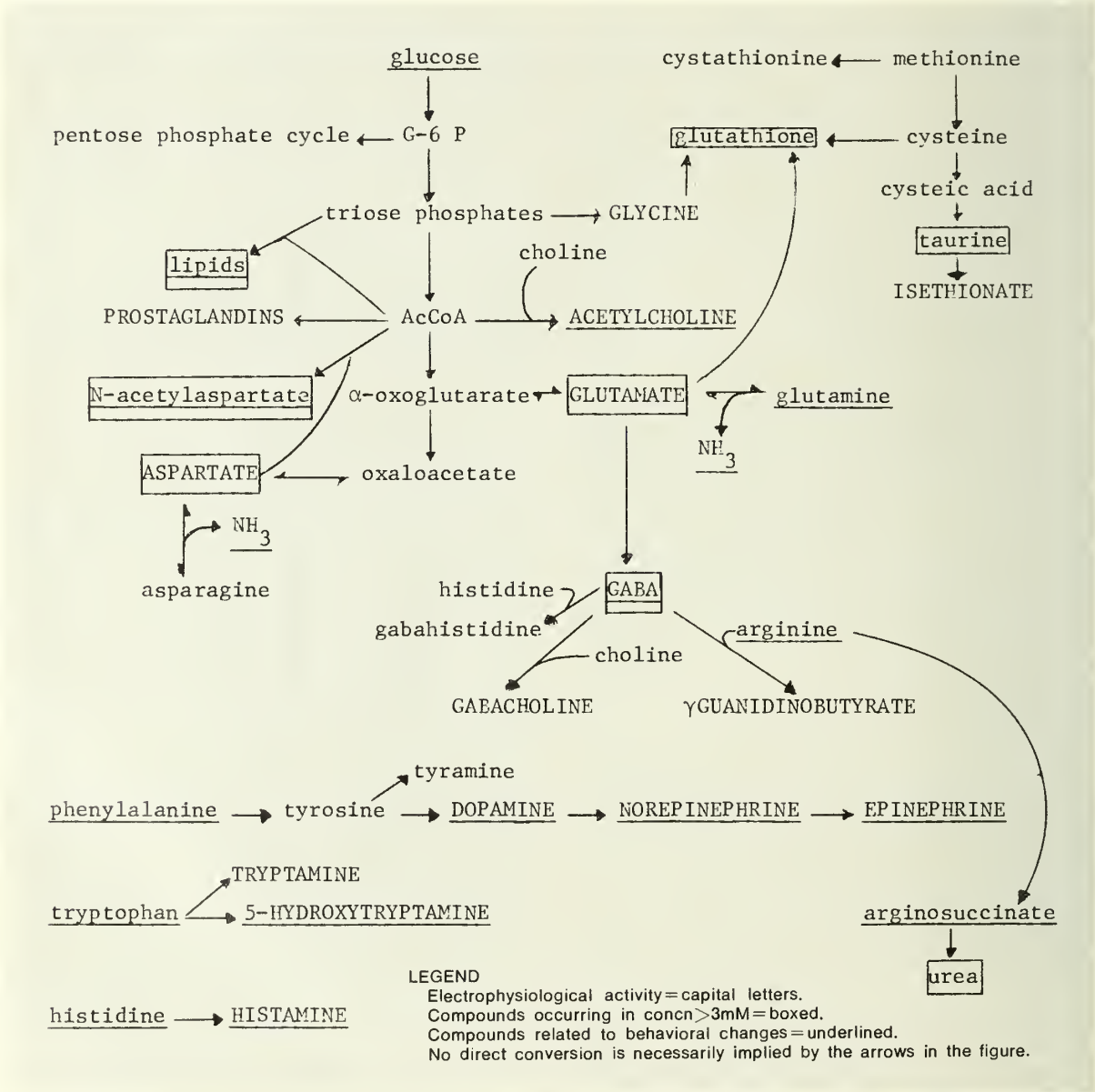


Figure 1.—Various interrelationships among compounds of neuropharmacological interest (adapted from Cooper et al[3] p 54).

teraction of cells of differing types.[71-74] No function is yet known for S100 protein, though S100 does undergo a conformational change when it binds Ca^{++}.[75] Claims have been made that the concentration of S100 is altered in experiments involving memory consolidation,[76] but this result is not widely accepted.[77] No function for the 14-3-2 protein was known either, until Marangos and co-workers showed there to be enolase activity.[78] The physical and chemical properties of this neuron-specific protein coincide with those independently described for the brain-specific isozyme of enolase, an enzyme in the glycolytic pathway. Electrophoretic comparison of brain enolase in 150 human autopsy samples has failed to reveal any differences,[79] just as similar analysis of each of the steps in glycolysis in brain showed that this essential "housekeeping" pathway of energy production is highly conserved.[80] Since there was great hope that the 14-3-2 protein would play some critical role in neuronal function, there may be some disappointment that it turns out to be only a brain-specific isozyme in glycolysis. Other proteins of interest[81] in brain include olfactory bulb protein, glial fibrillary acidic protein, nerve growth factor and the tau factor,[82] which promotes the polymerization of microtubular polypeptide units.

Neurotransmitters and Receptors in Human Psychopathology

The neurochemical studies reviewed thus far have extensive application to affective disorders (depression and manic-depressive illness), schizophrenia(s) and opiate addiction. In these diagnostic categories the probability of heterogeneous underlying mechanisms is so great that one must be extremely cautious in seeking "the cause" or "the treatment" for such disorders.[83] More likely, schizophrenias will prove as heterogeneous as anemias or mental retardation syndromes, with specific therapies. From the investigational point of view, such heterogeneity places a high value on exhaustive study of instructive families with more than one affected person, rather than on a series of unrelated patients.

The Biogenic Amine Hypothesis of Affective Disorders

According to the biogenic amine hypothesis,[84-86] at least some depressions are associated with an absolute or relative deficiency of norepinephrine (NE) or other biogenic amines (serotonin or dopamine) at functionally important receptor sites in the brain; mania, conversely, may be associated with excess of these amines. Pharmacologic agents which deplete NE from nerve terminals (reserpine) or interfere with its biosynthesis (α-methyltyrosine) precipitate depression in susceptible patients treated for hypertension. Drugs that enhance biosynthesis (L-dopa) can induce hypomanic states, and agents that prolong the action of biogenic amines by inhibiting intraneuronal monoamine oxidase (MAO inhibitors) or neuronal reuptake of transmitter released into the synapse (tricyclics, amphetamines) are effective antidepressants. Electroconvulsive shock also acts to increase NE turnover and tyrosine hydroxylase activity.[87] There may be genetically determined individual differences in any of these steps that could be shown by analysis of the effects of the pharmacologic agents.[83] For example, groups of depressed patients have been reported to be differentiated by their response to MAO inhibitors or tricyclics:[88] patients who responded to one class of antidepressant tended not to respond to the other; patients showed the same pattern of responsiveness during a subsequent episode of depression; relatives who had affective disorders shared the pattern of pharmacologic responsiveness or nonresponse. Studies of COMT in erythrocytes[89,90] and MAO in platelets[91,92] have claimed deficiencies or increases of these enzymes in groups of patients with depression. MAO in brain tends to increase with age, possibly contributing to the increasing prevalence of depression with age.[91,93] In fact, despite extensive studies, using various substrates of MAO, the relationships between MAO in platelets and MAO in brain remain to be worked out. Differences in substrate, inhibitor, immunochemical and electrophoretic characteristics have been found, but platelet MAO may still be identical with at least one form of brain MAO's.[94,95] Plasma DBH activity is not altered in patients with affective disorders or by treatment with lithium salts.[96] Lithium, which somehow modulates neurotransmitter effects, is clinically most effective in patients with bipolar manic-depressive illness, but has proved useful in some unipolar patients, as well.

The biogenic amine hypothesis has provided a useful framework for pharmacological observations in affective disorders. However, no primary lesions are known thus far. Direct enzyme assays and metabolite determinations have been fraught with difficulties and inconsistent results.[97] Even

the pharmacological interpretations have been challenged, since drugs that have prompt biochemical actions (tricyclics, for example) require many days for any behavioral change. Therefore, multiple-step compensatory or adaptive biochemical responses to these drugs have been proposed.[98] As an example of endogenous depression, a patient might have a genetic deficiency in COMT, compensation through reduced presynaptic firing rate, adaptive decrease in receptor activity, hyperresponsiveness to tricyclics, and then further adaptive decrease in firing rate and in tyrosine hydroxylase activity. Other studies have tried to distinguish the roles of the different biogenic amines. It is likely, based upon administration of specific precursors (L-dopa and L-tryptophan) and specific inhibitors of biosynthesis (alpha-methyl-tyrosine and p-chlorophenylalanine) that NE (and possibly DA) mediates changes in motor activity and that 5HT mediates changes in mood, as proposed by Lapin.[99] For example, L-dopa can induce hypomanic behavior in bipolar manic-depressives and helps some patients with retarded depressions; however, mood is not improved in patients with unipolar depression.[100,101] L-dopa may even decrease brain 5HT, which analyses of suicides suggest is already low in these patients.[101]

Even with these modifications, many additional influences, especially involving circulating hormones, must not be ignored. The major neuroendocrine disturbances in affective disorders are inhibition of growth hormone responses and hypersecretion of cortisol, both systems under regulation by biogenic amines. Many of these effects have been reviewed recently.[102]

The Dopamine Hypothesis in Schizophrenia

Theories and claims of experimental evidence of biochemical abnormalities in schizophrenia(s) have been legion, including speculations about roles for nearly all of the neurotransmitter compounds or their derivatives.[103,104] Dopamine is the neurotransmitter currently most strongly implicated in the actions of antipsychotic drugs and in the mediation of amphetamine-induced psychosis, the leading experimental model for schizophrenic psychosis. Phenothiazines reverse the primary symptoms of schizophrenia—the thought disorder, disturbances of affect and interpersonal withdrawal—while little affecting delusions, hallucinations, or nonspecific symptoms of anxiety and depression. It must be emphasized, however, that a dopamine hypothesis of antipsychotic drug action does not necessarily imply any primary role of dopamine in the pathogenesis of schizophrenia. There is no direct evidence of dopaminergic hyperactivity in schizophrenic patients; the major metabolite (homovanillic acid) has normal concentration in the cerebrospinal fluid, and serum prolactin, the release of which is strongly influenced by DA neurons, is also normal.[105]

Carlsson and Lindqvist[30] first suggested that phenothiazine and butyrophenone drugs blocked DA receptors, since these drugs increased concentrations of DA metabolites in brain, while the ineffective phenothiazine, promethazine, an antihistaminic drug, produced no such metabolic changes. The potency of antipsychotic phenothiazines is correlated with their conformational similarity to DA as it would fit into DA receptors.

In an attempt to differentiate antipsychotic actions from parkinsonian actions of phenothiazines, thioridazine and clozapine, potent antipsychotic drugs with relatively weak parkinsonian effects, have been investigated extensively in animals. These agents are highly active in several DA test systems.[104] Parallel studies of the affinity of antischizophrenic drugs for muscarinic cholinergic receptors show inverse correlation with their tendency to elicit extrapyramidal side effects;[106] clozapine and thioridazine act on DA receptors just like other phenothiazines but avoid the extrapyramidal side effects by a balancing blockade of ACh receptors in the striatum.

Amphetamines and related stimulant drugs in small doses can exacerbate the symptoms of schizophrenic patients and in large doses can elicit a psychosis clinically indistinguishable from acute paranoid schizophrenia.[107,108] These behavioral changes are reversed by phenothiazines and butyrophenones, the DA receptor-blockers. Amphetamine is now considered a far better mimic of schizophrenia, at least the acute paranoid type, than such psychedelic drugs as LSD, mescaline and dimethyltryptamine. Animal studies show that these stimulant drugs induce stereotyped, repetitive, apparently purposeless activities to the exclusion of normal behaviors. Such activities include sniffing, licking, biting and gnawing—while eating, grooming and sleeping are neglected.[109] Amphetamines, cocaine, phenmetrazine, and L-dopa all elicit a desynchronized electroencephalogram, with associated increase in reticular formation multiple unit activity, a reflection of

central nervous system stimulation. These electroencephalographic effects are entirely different from the hypersynchronous electroencephalographic changes induced by perception-distorting psychedelic agents. Local stimulation of DA receptors and chemical sympathectomy with 6-hydroxy-dopamine provide strong evidence that amphetamine-induced stereotypy is mediated by DA pathways.

This overview of research on schizophrenia presents the current focus on dopamine mechanisms. Work on urinary metabolites, including the "pink spot"[110] (dimethylphenylethylamine), plasma proteins and methylated derivatives of neurotransmitter metabolites in brain all have fallen into the background. However, the transmethylation hypothesis[111] might still apply in certain inborn errors of sulfur metabolism, especially those intrinsic to brain.[112] Given compelling evidence for genetic predisposition to schizophrenia, it is necessary to seek primary gene products, enzymes or polypeptide receptors, rather than just altered metabolic relationships. Dopamine-β-hydroxylase activity in brains of schizophrenics has been reported to be decreased,[113] possibly accounting for deficiency of NE in a NE-mediated reward system.[114] However, these observations have not been confirmable.[104,115] Other investigators have assayed monoamine oxidase (MAO) in platelets, a potential peripheral source of at least one type of brain MAO. MAO activity is reduced in platelets of schizophrenics[116] and in nonschizophrenic identical co-twins of schizophrenic twins.[117] Reduced MAO activity, presumably determined genetically, could cause relative excess of DA (and other biogenic amines), but the effect is not specific for schizophrenia. Assay of brain MAO has failed to show similar deficiency.[118]

Opiate Receptors: Toward an Understanding of Pain and Addiction

Morphine and its congeners have many important medical applications in patients with pain, cough, congestive heart failure, diarrhea and insomnia.[119] The agonist and antagonist compounds are potent and stereospecific, with stringent chemical requirements for activity, suggesting a role for selective receptor sites in the brain. If such receptors exist, there may be some naturally occurring substance in the brain with high affinity for these sites. Remarkable progress has been made in the past five years in demonstrating opiate receptors, peptides with morphine-like activity, and cellular phenomena *in vitro* that mimic addiction.[119,120]

The breakthrough was the preparation of highly radioactive potent opiates, so that tiny concentrations of opiate could be tested for specific, versus nonspecific, binding to extracts of brain or intestine.[121-123] Nonradioactive compounds were tested for displacement of ^{3}H-naloxone or ^{3}H-etorphine, which is 6,000 times more potent than morphine as an analgesic. Then stereospecificity of binding and correlation with analgesic potency were demonstrated; apparent discrepancies were attributable to differences in crossing the blood-brain barrier or metabolic activation (codeine). Sodium ion enhances binding of antagonists and dissociation of agonists in a manner which provides a rapid screen for much-needed mixed agonist-antagonist "nonaddicting" analgesics.[120]

Studies of the regional distribution of binding to opiate receptors in monkey and human brain[123] showed high binding in the amygdala, midbrain, periaqueductal gray, hypothalamus, medial thalamus and caudate nucleus. Within the cerebral cortex, frontal regions bound much more than precentral and postcentral gyri (motor and sensory cortex) or occipital pole; cerebellum and white matter had negligible binding. This distribution corresponds closely with the map of spinothalamic and spinoreticulodiencephalic pain pathways, except for the amygdala.[120] The amygdala is not associated with classical pain pathways, but affective components of pain and euphoric actions of morphine may be mediated by the amygdala and other limbic areas thought to regulate emotional responses. The periaqueductal gray matter is the area in which implantation of morphine most effectively produces analgesia, while the medial thalamus is the site where opiate antagonists best elicit withdrawal symptoms in addicted animals. More detailed mapping of opiate receptors has been achieved by radioautographic localization of binding of ^{3}H-diprenorphine, potent antagonist, in rat brain.[124] Binding was demonstrated in the locus coeruleus, but not in adjacent cells; small doses of morphine are known to slow firing rates of locus coeruleus cells, but not the adjacent cells.[125] In the substantia nigra, radioactivity was concentrated over the zona compacta, but not over the zona reticulata, corresponding to the distribution of dopaminergic cell bodies. Finally, binding was localized in the spinal cord and lower brain stem to the substantia

gelatinosa, an important way station for upward conduction of sensory information relating to pain.

Opiate receptor binding has been demonstrated in the central nervous system of all vertebrates, even primitive fish, but in no invertebrates. The receptor activity is fractionated with nerve endings, stimulating a search for an endogenous neurotransmitter or neuromodulator with specificity for these receptors. The search was promptly successful in several laboratories.[126-128] Brain extracts contain a substance that mimics the ability of morphine to inhibit electrically-induced contractions of smooth muscle preparations and which compete with opiates for specific receptor binding. The regional distribution of this substance, called enkephalin, is similar to that of the opiate receptor. Enkephalin consists of two pentapeptides (TyrGlyGlyPheMet and TyrGlyGlyPheLeu); peptides synthesized to have these sequences have identical biological properties. A third peptide with opiate agonist actions, larger and chemically dissimilar, has been extracted from pituitary. It is of interest that the methionine-enkephalin amino acid sequence occurs also in a protein called β-lipotropin in the pituitary.[126]

A valuable *in vitro* system for analysis of the cellular effects of narcotics has been developed.[74] Hybrid cells derived from fusion of mouse neuroblastoma and rat glial cell lines are rich in opiate receptors (300,000 receptors per cell). Binding of morphine results in a rapid inhibition of adenyl cyclase and a decrease in cyclic AMP in these cells,[129] as well as an increase in cyclic GMP.[130] Continued exposure to morphine caused a compensatory increase in adenyl cyclase activity, termed late positive regulation, restoring cyclic AMP levels to normal. This process makes the cells tolerant to morphine and also dependent upon the narcotic, since withdrawal of the drug or addition of a specific antagonist raises cyclic AMP levels to abnormally high values and secondarily reduces adenyl cyclase activity back to normal levels. The coupled inhibitory and late positive regulatory mechanisms provide a means of activating and deactivating neural circuits hours after the initial event. Methionine-enkephalin mimics these effects of morphine. There are no confounding effects on cell growth, number of receptors or affinity of receptors. Opiates also reverse the stimulation of adenyl cyclase by prostaglandin E_1 and adenine; cells exposed chronically to morphine are tolerant by the criterion that previously effective doses no longer antagonize the prostaglandin stimulation of adenyl cyclase.[129] These hybrid cells can form ACh-containing vesicles, choline acetylase, and apparent synapses and can respond with depolarization to DA. Morphine, in turn, is capable of inhibiting the response to DA.[131] Phosphodiesterase inhibitors (xanthines) produce a pseudoabstinence syndrome and oppose many of the immediate, therapeutic effects of morphine *in vivo*. Studies of cyclic nucleotides in rat brain indicate that opiates rapidly decrease cyclic AMP and increase cyclic GMP *in vivo*.[132]

These receptor assays and *in vitro* cellular systems may permit rapid progress in the elucidation of molecular mechanisms of addiction and of the recognition and affective component of pain.

Parkinson's Disease and Huntington's Disease

These two well-characterized disorders involve the basal ganglia and present with extrapyramidal signs.[133] In Parkinson's disease, discoveries of depigmentation in the substantia nigra and of dopamine deficiency in the striatum[134] set the stage for the demonstration of nigrostriatal dopaminergic fibers arising from cell bodies in the substantia nigra.[16,17] These axons are unmyelinated and the fibers have such small diameters that previous techniques had not uncovered this neuronal connection. The introduction and refinement of L-dopa therapy[135] was one of the most logical developments in medicine. However, many questions remain to be answered:[1,136] the cause of degeneration of cell bodies in the substantia nigra is still unknown; the DA deficiency accounts for akinesia and rigidity, but not for the third cardinal feature, tremor; patients may have notably differing severity of these three signs; and, very importantly, the basis for deterioration of intellectual performance in parkinsonian patients remains to be clarified.

L-dopa administration may introduce many effects beyond simply replacing DA deficits in the cells still able to convert dopa to DA and release DA. One of these effects is choreiform movements, leading to the suggestion that Huntington's disease may be mediated by a genetically-determined excessive responsiveness to normal levels of DA release in the striatum. Use of L-dopa as a provocative test for persons at risk for Huntington's disease is not recommended.[137] In both diseases drugs affecting either cholinergic or dopaminergic systems may be therapeutically effective, so the

balance between these systems and their interaction with GABAergic neurons must be examined and manipulated successfully. Direct assays for enzyme levels in human brain specimens have shown pronounced decrease in tyrosine hydroxylase in the substantia nigra, caudate and putamen, with some decrease in glutamic acid decarboxylase (GAD) and normal choline acetylase (ChA) in Parkinson's disease[138] and pronounced decrease in GAD with lesser loss of ChA in the extrapyramidal structures in Huntington's disease.[138-140] The enzyme loss in Huntington's disease seems to be correlated well with loss of cells and loss of tissue mass, histopathological characteristics of the disease. Huntington's disease is particularly important since it is due to a single abnormal autosomal gene. Patients with this disease have major psychiatric problems and occasionally are diagnosed as paranoid schizophrenics or manic-depressives, contributing to the probable heterogeneity of these major behavioral disorders.

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Candid Comments on Managing Moniliasis

The most frequent thing we see in the office is some form of moniliasis or low grade fungus infection. And in such situations, you've got to review many things. You've got to review such things as whether they [female patients] wear panty hose, whether they use colored toilet tissue, whether their bowel hygiene is correct, whether they like to sit in the tub for long periods of time or whether they like to sit around in a wet bathing suit for long periods of time. . . . The girls who get this should have their panties washed thoroughly and then boiled . . . that's the best way to try to correct it. Others caution, of course, about the use of vaginal sprays—the labial sprays. All of these things have been a boon to our business . . .

—J. BROOKS HOFFMAN, MD, *Greenwich, CT*
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Specialty Conference

Moderator
PHYLLIS A. OILL, MD

Discussants
STEVEN M. ROSER, DMD, MD
JEFFREY E. GALPIN, MD
IRWIN ZIMENT, MD
PAUL A. SELECKY, MD
JEROME SCHOFFERMAN, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Refer to: Oill PA, Roser SM, Galpin JE, et al: Infectious disease emergencies—Part III: Patients presenting with respiratory distress syndromes, *In* Infectious disease emergencies—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conference). West J Med 125:452-478, Dec 1976

Infectious Disease Emergencies

PART III:

Patients Presenting with Respiratory Distress Syndromes

PHYLLIS OILL, MD:* The third part of this symposium is concerned with those infectious disease processes that may present with symptoms of respiratory distress (see Table III-1). Also included in this part is a discussion about anaphylaxis, since this syndrome is often seen after the administration of antibiotics and may present as respiratory distress. The infectious diseases causing respiratory distress syndromes will be divided into major symptom complexes: upper airway obstruction, hypoxia caused by pneumonia, hypoventilation syndromes and pulmonary hemorrhage.

Before the first discussant speaks about those infections that affect the upper airways and may present as upper airway obstruction (UAO) I would like to point out the importance of distinguishing UAO from involvement of the lower airways. This syndrome can indeed be a medical emergency. Clinical signs such as inspiratory stridor, grunting, pronounced retraction of the accessory respiratory muscles and prolongation of the inspiratory phase of respiration should alert a physician to the possibility of UAO. Since complete obstruction of the airway can occur at any time, patients should be examined in the sitting position with immediate availability for intubation, cricothyrotomy or tracheostomy. Undue manipulation during the physical examination may precipitate complete airway occlusion.

With the above in mind Dr. Steven Roser will discuss infections of the upper respiratory tract.

Infections of the Upper Respiratory Tract

STEVEN ROSER, DMD, MD:† *Ludwig's angina* is a rare, severe cellulitis beginning usually in the submandibular space and extending to the sublingual and submental spaces. The process is not considered a true Ludwig's angina unless all four spaces are involved. Virtually all cases result from an infected mandibular molar[1] but may also result from a penetrating injury to the floor of the mouth or from osteomyelitis of the mandible.

The first symptoms are usually related to dental pain but a rapidly developing diffuse board-

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Part III of a five part symposium. Part I published in July 1976. Part II in August 1976. Parts IV-V to be published in subsequent issues.

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†Assistant Chief, Division of Oral Surgery, Harbor General Hospital; Assistant Professor of Oral Surgery, UCLA School of Medicine.

ABBREVIATIONS USED IN TEXT

(A-a)Po_2 = alveolar-arterial oxygen tension difference
ADH = antidiuretic hormone
Ara-A = adenine arabinoside
Ara-C = cytosine arabinoside
ARDS = adult respiratory distress syndrome
ARF = acute respiratory failure
c-AMP = cyclic adenosine monophosphate
CHF = congestive heart failure
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
ERV = expiratory reserve volume
FIo_2 = fractional concentration of oxygen in inspired gas
FRC = functional residual capacity
Pa co_2 = arterial partial pressure of carbon dioxide
Pa o_2 = arterial oxygen partial pressure
PEEP = positive end-expiratory pressure
$P_{\bar{v}}o_2$ = mixed venous oxygen tension
SRS-A = slowly reacting substance of anaphylaxis
TTA = transtracheal aspirate
UAO = upper airway obstruction
V_D/V_T = dead space-tidal volume ratio

like swelling on the floor of the mouth is present. There is a difficulty in eating and swallowing and patients usually have a rather high fever and a moderate leukocytosis. The disease may progress to involve the neck and be accompanied with edema of the glottis. Elevation of the tongue and edema of the glottis can lead to severe respiratory obstruction and death by suffocation. The infection may spread to the parapharyngeal space.

Most cases of Ludwig's angina are mixed infections with aerobic and anaerobic streptococci virtually always present. Fusospirochetes and other oral organisms have been isolated on various occasions.

Treatment should be directed toward localizing the infection and monitoring the patient closely for airway obstruction. Despite Ludwig's angina being a mixed infection, virtually all cases respond to high doses of parenteral penicillin. If signs of respiratory distress are observed before localization has occurred, a tracheostomy should be done. However, if localization has occurred, use of a nasoendotracheal tube will generally suffice to maintain a patent airway while the edema resolves after an incision and drainage procedure is carried out. The incision and drain-

TABLE III-1.—*Infectious Diseases Presenting as Respiratory Distress Syndromes*

Upper Airway Obstruction
- Ludwig's angina
- Parapharyngeal or retropharyngeal abscess
- Acute supraglottic laryngitis (epiglottitis)
- Acute laryngotracheobronchitis (croup)
- Diphtheria
- Anaphylaxis

Hypoxia with Severe Pneumonia
- Bacterial pneumonia
  - *Pneumococcus, Staphylococcus*
  - *Klebsiella, Pseudomonas,* other Gram-negative organisms
  - Aspiration
- Viral pneumonia, i.e. influenza
- Opportunistic infections, i.e. Pneumocystis carinii
- Fungal infections
- Tuberculosis
- Infective endocarditis (right sided)*

Pulmonary Hemorrhage
- Lung abscess
- Tuberculosis
- Fungal infections

Hypoventilation Syndromes
- Guillain-Barré
- Poliomyelitis
- Rabies
- Tetanus
- Botulism
- Tick paralysis
- Diphtheria
- Neuromuscular blockade associated with antibiotic administration

*Discussed in Infectious Disease Emergencies, Part II: Patients Presenting with Cardiac Decompensation and Circulatory Insufficiency (Shock).

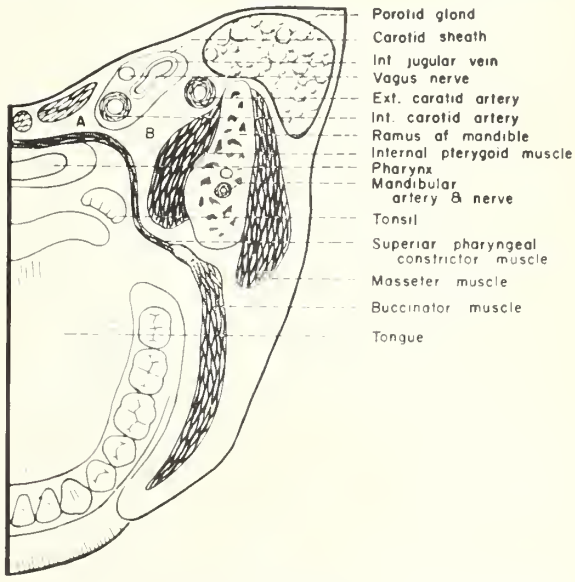

Figure III-1.—Horizonal section through the head at the level of the mandibular occlusal plane. The parapharyngeal spaces are indicated: **A**, retropharyngeal space, **B**, lateral pharyngeal space. (Reproduced by permission from: Shafer WG, Hine MK, Levy BM: A Textbook of Oral Pathology, 3rd Ed. Philadelphia, W B Saunders, 1974, p 463.)

age should be done in both the submandibular and submental areas and care taken to drain above the mylohyoid muscle.

Parapharyngeal Abscess

The lateral pharyngeal space is bounded anteriorly by the buccopharyngeal aponeurosis, the parotid gland and the pterygoid muscles; posteriorly by the prevertebral fascia; laterally by the carotid sheath, and medially by the lateral wall of the pharynx (see Figure III-1). Infection of the space may be by way of vascular or lymph channels from the tonsils, pharynx, nose, sinuses, adenoids, lymph nodes, mastoid or petrous bone. It usually begins as a cellulitis involving the anterior portion of the space with an abscess forming later in most of the cases. Infection may spread to the posterior part of the space which contains the carotid sheath. Thrombosis of the jugular vein, erosion of the carotid artery leading to fatal hemorrhage and mediastinitis are potential complications resulting from infections in the area.

A patient will usually note symptoms four to seven days after the infection has begun. Pain, usually referred to the ears, dysphagia and trismus are the most prominent symptoms. On examination of the oral cavity, displacement of the lateral pharyngeal wall without swelling of the tonsil is seen, which helps differentiate infections in the lateral pharyngeal space from a peritonsillar abscess. Fever, adenitis and leukocytosis are usually present. A lateral radiograph of the neck can aid in diagnosis when it shows displacement of the trachea anteriorly.

The bacteria involved are usually hemolytic and nonhemolytic streptococci; fusiform bacilli, pneumococci and staphylococci have also been implicated.

Therefore, high dose penicillin is the drug of choice. Bed rest and hot moist rinses are important adjunctive measures before localization. Once localization has occurred drainage of the abscess is necessary. This may be done through an intraoral or extraoral approach. Without appropriate drainage respiratory distress can occur from either mechanical obstruction or strangulation from sudden rupture of the abscess, especially in the young.

Retropharyngeal Abscess

The retropharyngeal space is bounded anteriorly by the wall of the pharynx, posteriorly by the prevertebral fascia and laterally by the lateral pharyngeal space and carotid sheath (see Figure III-1). It extends from the base of the skull along the prevertebral space to the posterior mediastinum. However, the attachment of the superior constrictor at the second cervical spine usually confines the abscess above it. An abscess in this area is uncommon. Factors leading to infection of this space are suppurative nodes, injuries and foreign bodies to the posterior pharyngeal wall and extension from infections of the parapharyngeal space. The bacteria involved are the same as those implicated in parapharyngeal abscesses.

A patient is usually first made aware of an infection in this area by painful swallowing. If the swelling is large enough, choking respiration or even dyspnea can occur. Cervical adenitis, cough, fever and leukocytosis are present. On examination of the oral cavity a smooth bulging mass will be seen displacing the buccopharyngeal fascia forward impinging on the pharynx. A lateral radiograph of the neck will show an anterior bulging of the posterior pharyngeal wall.

The danger of a retropharyngeal abscess in very young patients is chiefly due to suffocation and strangulation upon spontaneous rupture of the abscess. Older patients can usually manage the sudden drainage of pus because of better pharyngeal and cough reflexes. Other complications can include spread to the posterior mediastinum, meningitis, hemorrhage secondary to erosion into vessels, pressure on the epiglottis and larynx secondary to edema and aspiration of infected material.

Most of these cases can be treated with antibiotics, only if therapy is commenced early. Delay in treatment results in suppuration with fluctuation. When this occurs surgical intervention is mandatory. Obstruction of the airway demands immediate drainage. Precautions must be taken to prevent aspiration when draining these abscesses. Occasionally the edema and inflammation will lead to respiratory embarrassment before localization. In these cases a tracheostomy is best carried out early.

Acute Supraglottic Laryngitis or Epiglottitis

Acute supraglottic laryngitis or epiglottitis is a potentially lethal disease in children. It occurs not uncommonly in adults.

The pathophysiology involves a severe cellulitis of the tissues of the epiglottis and aryepiglottic folds. Because of the relatively small size of the

supraglottic larynx in children, small amounts of swelling predispose to obstruction. Thick inspissated secretions complicate the obstruction from edema. Hemophilus influenzae type B has been the bacteria cultured most consistently,[2] although infrequently other bacteria such as Staphylococcus aureus and hemolytic streptococcus have been isolated.

The course of the disease is usually rapid, progressing from mild upper respiratory tract infection type symptoms to almost complete respiratory obstruction over a period of 6 to 12 hours.[3,4] The disease usually begins with fever and malaise, with dysphagia as an important early symptom. The patients tend to remain quiet, concentrating on breathing. A typical presentation is a child sitting, leaning forward with an open mouth and tongue protruding to facilitate breathing. Compared with croup, the respirations are quiet because any increase in the effort to breath results in the edematous epiglottis acting like a ball valve which will completely obstruct the larynx on each inspiratory effort. As the edema progresses, soft tissue retraction, restlessness and cyanosis appear. If treatment does not intervene, respiratory arrest will occur.

On examination of the oral cavity the oropharynx will be seen to be somewhat injected with pooling of secretions. With depression of the tongue, a cherry red, edematous epiglottis can be seen projecting over the posterior tongue. Extreme caution must be exercised while carrying out this maneuver since this examination alone can result in complete obstruction. Direct laryngoscopy is contraindicated unless personnel and equipment are available for emergency intubation or tracheostomy since the procedure can also easily precipitate obstruction.

If visualization of the epiglottis for confirmation of epiglottitis cannot be accomplished, a lateral radiograph of the neck may show there to be characteristic supraglottic swelling. A radiograph of the chest is always indicated because atelectasis and pneumonitis may accompany this disease.

These patients must be admitted to hospital immediately and placed in an intensive care unit with appropriate equipment for airway maintenance by the bedside. Since it is always impossible to predict in which patients complete airway obstruction will develop, and since the morbidity and mortality rate is significant, many authors feel a tracheostomy is completely justified as a routine procedure.[4,5] A tracheostomy should be done in any case where there is any degree of obstruction or whenever experienced personnel are not available for observation. An alternative method of providing an airway, which requires experience, is prolonged nasotracheal intubation.[6] If respiratory obstruction is not one of the presenting signs, vigorous conservative therapy may obviate having to establish an airway. While being observed, if any respiratory symptoms or obstruction occur, an endotracheal tube should be inserted immediately followed by a tracheostomy done under more orderly circumstances.

Conservative treatment includes use of parenteral fluids, humidity, oxygen and mucolytic agents. Patients should be kept quiet to prevent anxiety. Antibiotics should be instituted. Administration of ampicillin, 150 to 200 mg per kg of body weight per day, is standard therapy. Chloramphenicol is an acceptable alternative if a patient is allergic to penicillin. Steroids may be of value in limiting progression of the inflammation and edema.

Acute Laryngotracheobronchitis or Croup

Acute laryngotracheobronchitis, or croup, is a severe acute inflammatory disease of the larynx, trachea and bronchi usually involving children under five years of age. The most critical feature of this disease is the edematous swelling of the conus elasticus with narrowing of the infraglottic area (see Figure III-2). An intense inflammatory

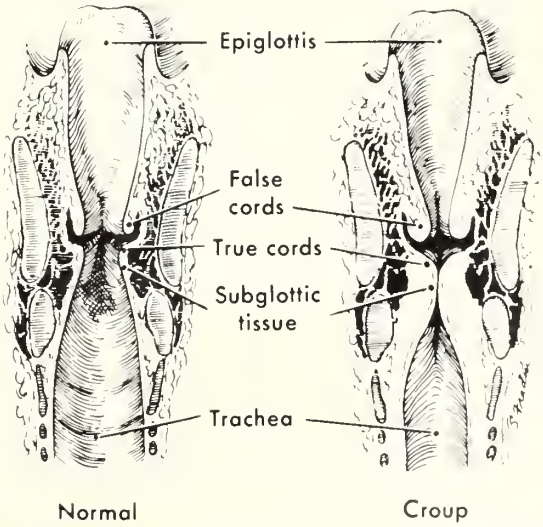

Figure III-2.—Schematic diagram of larynx and trachea in viral croup as compared with normal appearance. (Reproduced by permission from: Krugman S, Ward R: Infectious Diseases of Children and Adults, 5th Ed. St. Louis, C V Mosby, 1973, p 208.)

reaction of the mucosa with loss of epithelium and an outpouring of thick secretions accompanies the swelling. Therefore, obstruction results from both secretional and mechanical factors. The infectious agents are predominantly the respiratory viruses, parainfluenza type 1, 2, 3 and influenza A_2 and B.[7] Secondary infection with Gram-positive bacteria may occur.

The disease usually begins as a mild upper respiratory tract infection. This is followed by a croupy, barking, nonproductive cough. The onset of the cough is usually at night. The course may be either self-limiting or progress to respiratory obstruction. Although the onset and progression is gradual, occasionally sudden deterioration occurs. Respiratory difficulty is characterized by chest wall retraction, prolonged inspiratory phase and expiratory wheezing. Also, malaise, tachycardia, fever and restlessness are usually present.

The diagnosis is based on clinical presentation and findings of physical examination. On examination of a child with this disease, nasal discharge is noted, and infected pharynx with normal appearing epiglottis, tachypnea and inspiratory stridor. A lateral radiograph of the neck can be useful by showing the characteristic infraglottic narrowing.

Management is similar to that in supraglottic laryngitis—which includes humidification, hydration, oxygen and antibiotic therapy. Use of sedatives, which may mask signs of respiratory failure, and narcotics, which suppress the cough reflex, is to be avoided. The child should be spared all needless procedures. The use of steroids is debatable with some authors suggesting that they are ineffective and enhance susceptibility to infection,[8,9] and others finding that if steroids are given in adequate doses this may shorten the length of the disease and the stay in hospital.[10,11] At present the routine use of steroids in the disease is not justified. The final decision will rest with the responsible physician, who must weigh the relative merits and risks of therapy for a particular patient.

Although the cause of this disease is viral, when the patient is febrile with a leukocytosis, use of antibiotics should be considered.[12] Ampicillin, 150 to 200 mg per kg of body weight per day, is the drug of choice.

As in epiglottitis, vigorous conservative therapy will usually be sufficient in most of the early cases. However, any sign of respiratory obstruction such as increased respiratory rate, retractions, restlessness, tachycardia and cyanosis will make a tracheostomy necessary. This is necessary in approximately 7 percent of all cases.[13]

Diphtheria

Diphtheria is now an uncommon acute infective process involving all or part of the upper respiratory tract. It occurs in children over six years of age. The pathophysiology involves a superficial infection involving the mucous membranes. Epithelial necrosis is accompanied by an outpouring of serum and this agglutinates into a firmly attached membrane. The bacteria elaborates an exotoxin which produces more necrosis. This exotoxin when absorbed systemically attacks heart muscle and peripheral nerves. Death may result from airway obstruction or heart failure.[14]

The disease is caused by Corynebacterium diphtheriae, a Gram-positive organism of which there are three types. The gravis type is responsible for diseases in North America. The usual spread is by droplet, but this organism can change from a nonvirulent strain to a toxin producing virulent form which probably accounts for isolated cases.[15] Immunization has kept this disease to a minimum.

The incubation period is from one to six days. The onset is characterized by a slight sore throat, malaise and low grade fever. On examination of the oral space the presence of a grayish white membrane on the tonsils, pharyngeal wall or larynx will be noted. Cough, hoarseness, stridor and progressive signs of respiratory obstruction can occur. This is related to both edema and the membrane. Sudden asphyxia can occur when a piece of the membrane dislodges and becomes entrapped in the larynx. Cervical adenitis is usually present and, if pronounced, gives a characteristic bull neck appearance.

Diphtheria must be considered in the differential diagnosis of any membranous pharyngitis or laryngitis. If microscopic examination of a piece of the membrane shows the organism, that makes the diagnosis.

Treatment includes administration of antitoxin, penicillin and oxygen, and continuous monitoring of the patient's respiratory status. If symptoms of respiratory obstruction are pronounced, a tracheostomy is indicated. Bronchoscopy should be done first so that any membrane in the trachea or bronchi may be removed as well as to provide an airway during the tracheostomy.

DR. OILL: A further discussion of the effects of diphtheria exotoxin will be presented later in this session under the topic of hypoventilatory syndromes. In addition, more extensive reviews of oral pathology and infectious diseases of children have been published.[16,17]

The next area of consideration will be those intrathoracic processes which often manifest as respiratory distress associated with hypoxia. Dr. Jeffrey Galpin will discuss the varied causes of infective pneumonitis and Dr. Irwin Zimcnt will then speak about the physiology and management of severe pneumonia.

Infectious Pneumonias

JEFFREY GALPIN, MD:* Pathologists may describe pneumonia in terms of "interstitial," "alveolar" or "acute necrotizing" processes, while radiologists focus on anatomical terminologies of "lobar," "peribronchial" or "cavitary." Finally, clinicians may direct their assessment of pneumonia in the context of "overwhelming," "atypical" or "opportunistic." However, far more useful is an effort to describe infectious pneumonia as due to a specific etiologic agent with directed, specific therapeutic modalities.

When a person presents to an emergency department with respiratory distress several factors must be considered. Epidemiological factors like age, setting of the infection and the season of the year can be helpful (see Table III-2). Clinical findings such as underlying diseases, duration and severity of illness, and particular signs and symptoms also may aid in diagnosis. Finally, the radiologic characteristics, peripheral leukocyte count and description of sputa and transtracheal or thoracic aspirate greatly assist in allowing an intelligent approach toward treatment.

Pneumococcal Pneumonia

In a middle-aged or elderly person in whom pharyngitis, chills, fever and pleuritic pain have occurred for several days associated with dyspnea, tachypnea and productive bloody or greenish mucopurulent sputum, one must seriously consider a diagnosis of pneumococcal pneumia, now known as Streptococcus pneumonia. This organism accounts for a minimum of 80 percent of the

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TABLE III-2.—*Key Associations of Pneumonia*

Organism	*Age*	*Leukocyte Count*	*Specific Underlying Disease*	*Other Complications*
Pneumococcus	Severe in old	N↓↑	Hemoglobinopathies, multiple myeloma, CHF, alcohol, diabetes mellitus	Endocarditis, meningitis, arthritis
Staphylococcus	Old	↑	COPD, CHF, drug abuse, viral pneumonia, diabetes mellitus, granulocytopenia, cystic fibrosis	Meningitis, endocarditis, abscess
Klebsiella	Old	↑	COPD, aspiration, drug abuse, CHF, diabetes mellitus, hospital-acquired infections	Chronic pneumonia, abscess, sepsis
Pseudomonas	..	↑↓	Aspiration, hospital-acquired infections, drug abuse, granulocytopenia	Multiple abscesses, sepsis
Influenza	..	N↑↓	COPD, CHF, mitral valve disease, pregnancy	Secondary bacterial pneumonia, encephalitis, myocarditis
Pneumocystis carinii .	..	N	Lymphoproliferative diseases with immunosuppressive therapy	.....
Herpes viruses	Very young	N	Lymphoproliferative diseases and other neoplasms, diseases where cytotoxic drugs and steroids used	Dissemination to all organ systems
Anaerobes	..	↑	Aspiration, alcohol, seizures, dysphagia, altered state of consciousness	Endocarditis, abscesses, empyema, sepsis
Mycoplasma	Young	N↑↓	.....	Neurologic, gastrointestinal, dermatologic
Psittacosis	..	N↑↓	.....	Encephalitis
Q Fever	..	N↑↓	.....	Hepatitis, endocarditis
Coccidioidomycosis ..	..	N↑↓	Immunosuppression	Meningitis, bone, other metastatic sites
Tuberculosis	..	N↑↓	Immunosuppression, bacterial pneumonias	Miliary or distant infection in almost any organ
Nocardia	..	↑↓	Immunosuppression	.....

COPD = chronic obstructive pulmonary disease CHF = congestive heart failure N = normal

bacterial pneumonias seen.[18] Herpes labialis, an ileus or splinting of the chest due to pleurisy, may be associated with this pneumonia. Signs of lobar consolidation are found on physical examination, and fine crackling rales and pleural friction rub are common. The patient's temperature may range from 102 to 106°F and febrile peaks often occur in the late afternoon.

On a Gram stain of the sputum, many polymorphonuclear leukocytes and Gram-positive encapsulated, lancet-shaped diplococci singly or in short chains are seen. More than 30 organisms seen in a single high-power microscopic field correlate with high counts from smears of the lung at autopsy and therefore a poorer prognosis. A web-like appearance on Gram stain suggests the presence of large amounts of soluble specific capsular substance which frequently is indicative of type III organisms.[18] When sputum is not expectorated or oropharyngeal infection obscures the diagnosis, then a transtracheal aspirate (TTA) study is required.

Leukocyte counts range to 40,000 per cu mm and there is usually a shift to the left. A normal leukocyte count or leukopenia often occurs in the fulminant or bacteremic infection. Jaundice occurs not infrequently, being due to hemolysis from pneumolysin within the lung and liver.[18]

Radiologically, a classic lobar pneumonia is seen especially in one lower lobe although multiple lobes may be involved. Cavitation, empyema and effusion occur but are uncommon.

Certainly alcoholism, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes mellitus, SS and SC hemoglobinopathies increase the morbidity and mortality of pneumococcal pneumonia. Patients with bronchogenic carcinoma, multiple myeloma, asplenism and hypogammaglobulinemias are also predisposed to this illness. Treatment with 600,000 units of penicillin G given intravenously every six hours is the therapy of choice. Other effective agents in this disease are the cephalosporins, clindamycin and erythromycin. Mortality and bacteremia increase with age.[19] Bacteremias may result in septic arthritis, meningitis, endocarditis, empyemas of the gallbladder, peritonitis and disseminated intravascular coagulation. Pneumococci are delicate organisms and the culture media should be used directly at the bedside. Carbon dioxide is required by many types of pneumococci and immediate incubation is necessary. Even without a bacteremia pneumococcal antigen can be detected rapidly in serum by the use of immunoelectrophoresis and polyvalent antipneumococcal serum.

Staphylococcal Pneumonia

Staphylococcus aureus represents about 1 percent of all pneumonias and occurs sporadically except during influenza or measles epidemics.[20] With leukemia, collagen vascular disease or heroin or alcohol abuse there is greater susceptibility to this disease.

Multiple chills, high fever, dyspnea, cough and pleurisy occur early in the disease. Creamy sputa containing clusters of large Gram-positive cocci are characteristic. Most patients are very ill and vascular collapse is frequently seen.

Leukocytosis is frequently seen in these patients, although bacteremia may be uncommon. Blood cultures, however, must be obtained as in all suspected bacterial pneumonias. If a staphylococcal bacteremia does exist, the possibility of endocarditis or other metastatic complication must be strongly considered.[21]

The characteristic findings on radiologic examination include a patchy central or lower lobe infiltrate which may progress to abscess, empyema or pyopneumothorax. Signs of frank consolidation are rare while radiologic evidence of a pneumatocele are common.[18,22] Penicillin G, 1.5 million units, and methicillin, 1.5 grams, given intravenously every four fours should be administered until antibiotic sensitivity data are available. Patients allergic to penicillin should be given vancomycin, 2 grams administered intravenously in four divided doses every 24 hours, or cephalothin, 1.5 grams administered intravenously every four hours.

Patients presenting with staphylococcal pneumonia and bacteremia may also have associated cutaneous lesions such as subcutaneous abscesses, petechiae, Osler's nodes, urticaria, erythema multiforme or infected bullous eruptions. Other clues to the diagnosis may be a purulent otitis media, subcutaneous emphysema or suppurative parotitis.[23]

Klebsiella Pneumonia

Klebsiella is an organism usually acquired as a superinfection. Klebsiella occurs as normal oropharyngeal flora in 1 to 25 percent of people. Aspiration, especially related to ventilatory equipment or associated with the debilitated host, is a common predisposing factor in this illness.[24] This

organism invades the lungs after a preceding viral disease or in association with other pulmonary parenchymal disease. Chills, hectic fever, pleurisy, dyspnea and occasionally jaundice and emesis—especially in patients with predisposing illnesses such as alcoholism, diabetes, CHF, COPD and renal or neoplastic disease—must alert one to a possible Klebsiella pneumonia (see Table III-2). Clinical evidence of Gram-negative sepsis is not uncommon.

Profound prostration and sustained spiking irregular fevers are usually seen with this pneumonia. Physical findings are those of lobar consolidation with or without abscess. There is an acute loss of lung volume resulting from the necrotizing effects of this pneumonia. Therefore, the involved hemithorax may show an elevated diaphragm and ipsilateral tracheal shift.[25]

On studies of sputum many polymorphonuclear leukocytes and many Gram negative encapsulated rods are noted. Leukocytosis is frequent but a third of patients have leukopenia. Positive blood cultures may be present, and along with leukopenia, portend a worse prognosis.

On x-ray examination lobar consolidation is seen, or occasionally bronchopneumonia especially of the upper lobe. Bulging interlobar fissures and sharp borders of the infiltrate are characteristic. Multilobe involvement and abscesses occur in about 50 percent of patients.

Treatment involves using an effective aminoglycoside such as gentamicin, given intravenously at a dosage of 1.7 mg per kg of body weight every eight hours (providing renal function is normal) for at least 10 to 14 days or until parenchymal clearing occurs.

Chronic Klebsiella pneumonia is a distinct syndrome with patients presenting with several weeks of malaise, cough and occasional hemoptysis. X-ray studies show bronchopneumonia, bronchiectasis or radiological evidence of thin walled pulmonary cavities. The diagnosis is established by isolation of the organism from pulmonary secretions (most reliably by study of TTA as opposed to expectorated sputum). Long-term antibiotic therapy is frequently necessary for effective eradication of the infection. Not uncommonly surgical resection of the infected lung may be required if medical therapy alone is ineffective.

Pseudomonas Pneumonia

Pseudomonas pneumonia, like Klebsiella infection, occurs in a similar milieu—that is, secondary to aspiration, in superinfection, in burn patients, in immunosuppressed persons or in chronically ill patients. Patients present with dyspnea, fever and signs of infiltrative lung disease. On radiologic examination characteristically a necrotizing pneumonia with microabscess formation is shown. Studies of sputa show Gram negative rods. If bacteremia occurs, the prognosis is very bleak with a mortality of almost 100 percent.[26] Persons with leukopenia are particularly predisposed to Pseudomonas infections including pneumonia and bacteremia.[27]

Aminoglycosides with antipseudomonas activity, such as gentamicin, tobramycin or BB-K8 (Amikacin®), are the drugs of choice. Despite this therapy, the mortality is 25 to 60 percent.[28] Carbenicillin (30 to 40 grams per day) should be added to the regimen with pronounced leukopenia, presence of bacteremia, extensive pulmonary involvement or failure to respond to an aminoglycoside alone.

Influenza Pneumonia

Pneumonia due to influenza virus is generally seasonal and can reach epidemic magnitude. Since the pandemic in 1918 and 1919 there have been regular epidemics. The pandemic of 1957 to 1958 marked the appearance of the H2/N2 antigen subtype which resulted in more than 86,000 deaths in the United States. Since 1889 in the United States there have been 52 epidemics or pandemics.[29] Outbreaks are characterized by abrupt onset with a high incidence of rapid but irregular spread through communities. The peak is reached and passed in about one month.

A patient seen in the emergency department may complain of the onset of fever and chilliness, with episodes of sweating, headache and myalgias. Minor upper respiratory symptoms may precede the constitutional complaints. A nonproductive, painful cough and prostration are characteristic. Conjunctival irritation and minor nasal obstruction are frequent. Abdominal pain and diarrhea are rare.

Gram stain of the sputa is nondiagnostic and findings on radiological examination include a wide spectrum from normal lung fields to bronchopneumonic infiltrates progressing to true lobar consolidation. Neutrophilia may be seen initially, but usually leukopenia with a relative lymphocytosis is seen. In up to 75 percent of uncomplicated cases electrocardiographic changes of T wave inversion or depression are seen.

Persons with cardiopulmonary disease (such as COPD or rheumatic heart disease), pregnant women, and elderly and debilitated patients are predisposed to complication of this illness. These patients do poorly with primary influenza pneumonia and also secondary staphylococcal, pneumococcal or Hemophilus influenzae infections often develop. These susceptible persons are also more likely candidates for influenzal encephalitis, radiculitis, seizures, myocarditis with CHF or arrhythmias and primary hemorrhagic pneumonitis. These patients in whom secondary complications do develop are often quite ill when they seek medical care. Hypoxia is frequently pronounced and it is often difficult to determine if a superimposed bacterial infection exists. It is in these patients that a TTA study is indicated. Treatment with appropriate antibiotics should be carried out if bacteria are seen on Gram stain of the aspirate or cultures yield a pathogen. Amantadine hydrochloride is active against influenza type A primarily on a prophylactic basis; however, recent evidence indicates that the drug also possesses moderate therapeutic effects during the active infection.[30] Unfortunately, there is no completely adequate therapy for the viral pneumonia but certainly secondary infection and other complications must be anticipated and treated appropriately.

Pneumonias in the Altered Host

The discussion to this point has emphasized particular infective agents that comprise most types of pneumonia seen in patients presenting to an emergency department. The diagnosis and treatment of other types of pneumonia will now be approached in terms of certain underlying diseases and specific alterations in host defenses.

Aspiration Pneumonia and Lung Abscess

Aspiration must be suspected as the pathogenesis of pneumonia in a person brought to an emergency department with a history or findings of an altered state of consciousness and pulmonary infiltrate. Alcoholism, heroin addiction, cerebrovascular accidents, seizures, cardiogenic shock and encephalitis are typical examples. Additionally, abnormalities in swallowing or cough reflex predispose to aspiration. More than half of the patients with aspiration pneumonia will present with infiltrates in the dependent lobe of the lung reflecting a positional or gravitational pneumonia. About 20 percent of the patients will present with a necrotizing pneumonia defined as a suppurative infection characterized by multiple small cavities usually within a single pulmonary lobe. A third of patients expectorate putrid sputum and most present with an elevated leukocyte count and fever. Finally, the cause of lung abscess in about a third of patients with this disease is secondary to an episode of aspiration.[31,32]

The organisms involved are those normally found in the mouth. Therefore, the infection is usually polymicrobial and includes aerobic Staphylococcus aureus, Group A Beta hemolytic streptococci, Streptococcus pneumoniae, Klebsiella, Escherichia coli, Pseudomonas aeruginosa, Proteus species and anaerobic organisms like Bacteroides melaninogenicus, Bacteroides oralis, streptococci, Fusobacterium nucleatum, Clostridium and possibly Bacteroides fragilis.[33] Because the organisms are derived from the normal flora of the oropharynx, a sputum culture is of little value. Meaningful bacteriological data can only be obtained by examining secretions from the lower respiratory tract either by TTA study or transthoracic needle aspiration. Additionally, examination of pleural fluid (if present) is a reliable source for microbiological information. A mixed anaerobic and aerobic infection is found in most patients with aspiration pneumonias. Uncomplicated aspiration pneumonia occurring outside a hospital will usually respond effectively to parenteral penicillin in doses of 2 to 4 million units a day. Clindamycin, 600 mg given intravenously every eight hours, is an acceptable alternative. Aspiration occurring in hospital will generally necessitate additional therapy for aerobic Gram-negative rods (such as use of gentamicin) until cultural data become available or if the patient's condition deteriorates on single antibiotic therapy. The role of Bacteroides fragilis is unclear in aspiration pneumonia. If the organism is isolated from blood specimens or repetitively from respiratory secretions, therapy should include agents effective against these bacteria (such as clindamycin or chloramphenicol).

Primary lung abscess may develop secondary to aspiration. The most frequent sites for this lesion are identical to those of aspiration pneumonias and include the posterior segments of the upper lobes or superior segments of the lower lobes, or the basilar segments of the lower lobes. Common symptoms include cough with putrid sputum production, pleuritic chest pain and

hemoptysis. Weeks of fever, malaise, anemia and weight loss are also reported.[34,35]

Most evidence points to a polymicrobial flora with anaerobes predominating within the lung abscess. These include Fusobacterium nucleatum, Bacteroides melaninogenicus, Peptostreptococcus, Peptococcus and Eubacteria.[33] Chemotherapy should be with either parenterally given penicillin G, 4 to 8 million units a day, or clindamycin 600 mg given intravenously every 6 to 8 hours. Several weeks to months of chemotherapy and good pulmonary drainage may be required until findings on studies of sputa return to normal and the cavity has resolved to a significant degree. Rarely, surgical resection is required after failure of medical therapy. The size of the cavity and duration of symptoms before therapy are important prognostic factors.

Necrotizing pneumonias as well as lung abscess may occur secondary to E. coli, Proteus species and Serratia, and less commonly with organisms such as Nocardia,[36] Actinomyces, Aspergillus[37] and Mycobacteria tuberculosis. Moreover, other disease processes like bronchogenic carcinoma, right-sided endocarditis and septic emboli from other sources may produce similar clinical features. A patient may present with hemoptysis or frank pulmonary hemorrhage secondary to the necrotizing process.

Finally, an acute empyema may result from extension of a necrotizing pneumonia, abscess or, in granulomatous disease, from a mediastinal lymph node. Findings here are identical to those in lung abscess and include intermittent fever, sweating, chest pain, anemia, leukocytosis and weight loss. Treatment includes use of appropriate antimicrobial agents, provision of adequate drainage and obliteration of the dead space.

Pneumonia in Immunosuppressed Patients

Pneumocystis carinii pneumonia should be considered in immunosuppressed patients in whom an insidious onset of progressive dyspnea and nonproductive cough develops, frequently without pulmonary auscultatory abnormalities.[38,39] Hypoxia is seen especially in later stages of this disease. Fever is not necessarily a component. Classic radiologic evidence of a pneumonia need not be present but in progressive cases bilateral interstitial features are frequently seen in the lower lobes. Definitive diagnosis is made by identification of the pathogen histologically by silver methenamine stain on lung tissue obtained by biopsy, by pulmonary lavage or occasionally by bronchial brushings. The diagnosis should be confirmed as soon as possible, and if a high index of suspicion exists therapy with pentamidine isethionate (4 mg per kg of body weight per day given intramuscularly) should be carried out. Administration of pyrimethamine and sulfadiazine is an alternative therapeutic regimen. Pneumocystis carinii may be found associated with other infections like the cytomegalovirus.

In any immunosuppressed patient presenting with bronchopneumonia a localized or disseminated cytomegalovirus or herpes infection may be present. Viral cultures of sputa, TTA studies, buffy coat of the blood and tests of urine and stool specimens should be done. Urine sediment can be examined for inclusion bodies to aid in the diagnosis. Other signs of dissemination such as neurologic or gastrointestinal disturbances should be carefully sought. If these viral infections are strongly considered, then immunosuppressive drugs should be discontinued or tapered if possible. The efficacy of adenine arabinoside (Ara-A) and cytosine arabinoside (Ara-C) in the treatment of these viral infections has not been clearly delineated.

Additionally, in an immunosuppressed patient, other opportunistic agents must be considered as a potential cause of pneumonia. Infectious granulomatous disease (such as tuberculous or fungal), Nocardia, Actinomyces, Gram-negative bacilli, or even Toxoplasma are agents that fall into this category.

General Comments

Certain underlying diseases may suggest specific infective pneumonias. For example, the presence of multiple myeloma in a patient should make one suspicious of pneumococcal pneumonia and less commonly Gram-negative pneumonias, unless immunosuppressive therapy is being carried out. Patients with sickle cell disease are also predisposed to pneumococcal pneumonia. In persons with lymphoma and pneumonia studies must be done for common pathogens—but also for organisms such as cytomegalovirus, herpes simplex and zoster,[10,41] Toxoplasma[42] and Aspergillus, as well as Mycobacteria. Additionally, in a patient receiving high dose steroids there is an increased risk of a herpes virus, toxoplasma, Pneumocytis carinii or fungal pneumonia developing.

Bacterial endocarditis should be suspected in patients in whom there is evidence of multiseg-

mental bronchopneumonia or necrotizing pneumonia. More than half of the persons with right-sided endocarditis present as having multisegmental pneumonia and often no cardiac murmur may be present. Furthermore, in persons with septic or suppurative thrombophlebitis frequently there are signs of septic emboli to the lung. In many of these patients, other evidence of endocarditis may be present, such as hematuria, cutaneous or conjunctival petechiae or metastatic abscesses.

Bronchopneumonia in a young person is most frequently due to pneumococcal, mycoplasmal or adenoviral infections.

Unusual associations—such as exposure to specific animals—should bring to mind such pneumonic entities as psittacosis or Q fever. Geographic settings may make it more likely to include histoplasmosis or coccidioidomycosis in the differential diagnosis. Finally, personal contacts may suggest diseases such as tuberculosis, and social habits such as heroin addiction or alcoholism may suggest their own list of infective pneumonias and complications.

Although the diagnosis of a specific infective pneumonia is difficult, especially in an emergency situation, a logical approach, utilizing a knowledge of the above diseases combined with a good history, physical examination and limited laboratory evaluation, is possible (see Table III-3).

The Physiology and Management of Severe Pneumonia

IRWIN ZIMENT, MD:* Most infectious diseases that affect the lungs result in difficulties in oxygen transportation through the airways, and thereby cause hypoxemia. Bacterial infections lead to consolidation, and the resultant alveolar filling places a barrier between the gas in the airways and the blood in the alveolar capillaries. Many other infections, particularly those caused by respiratory viruses, result in interstitial inflammation; if this is not extensive, then there is relatively little total impedance to gaseous exchange. However, many interstitial infections involve the whole lung, and the generalized process leads to pronounced hypoxemia, which rapidly worsens as the inflammatory process spreads into the airways and alveoli.

Pneumonic infections may be localized, causing lobar consolidation, or more generalized, resulting in multilobar pneumonia or bronchopneumonia. The infecting organism may result primarily in an alveolar or an interstitial reaction, but in severe cases there is a mixed pattern. An extensive multilobar infection tends to produce a proportionally severe physiologic derangement, whatever the particular infecting agent may be. If a patient has abnormal lungs to begin with or if secondary cardiopulmonary complications develop, death from hypoxemia may supersede. Severe pneumonia is characterized by toxemia and hypoxemia, and the underlying abnormalities in the lung consist of interstitial inflammation with edema, capillary damage and airway occlusion by a conglomeration of mucus, organisms, inflammatory cells, blood and serum.

The major problem in overwhelming pneumonia is hypoxemia; numerous individual factors contribute to this abnormality.[43] Apart from the increased separation between airway gas and capillary blood caused by infected mucus and bronchioalveolar secretions, the mechanics of breathing and the distribution of blood flow are adversely altered. The fever, toxemia and increased metabolic demands result in additional tissue demands for oxygen, while pleural pain and the increased stiffness (that is, decreased compliance) of the lungs result in additional work because of the inefficient, rapid, shallow breathing, which further increases oxygen needs. In the lungs, the inflammatory reaction results in rela-

TABLE III-3.—*Diagnosis of Pneumonia by Location and Form*

Location:	
Lobar consolidation	Diplococcus
Bulging right upper lobe fissure	Klebsiella
Patchy central infiltrates	Staphylococcus or viral
Patchy bronchial infiltrates	Mycoplasma
	Influenza
	Q fever
	Psittacosis
Form:	
Granulomas or multiple nodules	Tuberculosis
	Histoplasmosis
	Coccidioidomycosis
	Klebsiella
Abscess	Anaerobes, aspiration
	Gram-negative rods
Empyema	Anaerobes
	Staphylococcus
	Gram-negative rods
Necrotizing pneumonias	Anaerobes, aspiration
	Gram-negative rods
	Nocardia
Microabscesses	Pseudomonas

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tive vasodilation in the involved areas where gaseous exchange is poor: the increased blood flow to poorly ventilated zones constitutes a right-to-left shunt, with a further increase in systemic hypoxemia. Further circulatory derangement will occur with toxic capillary damage, localized thrombosis, disseminated intravascular coagulation, heart failure or adverse fluid balance; the existence of all these complications characterizes the severe respiratory insufficiency of the so-called adult respiratory distress syndrome (ARDS) or acute respiratory failure (ARF) which might occur in overwhelming pneumonia. This condition is similar to the posttraumatic respiratory syndrome, which has been the subject of intensive study; some of the following discussion is based on the work of surgical researchers.[44]

Physiologic Findings in ARDS (Table III-4)

Patients with severe pneumonia are not in a condition to permit routine pulmonary function testing, but many abnormalities in function can be determined at the bedside or can be deduced from clinical and radiologic findings. Usually, studies of the arterial blood gases provide the most critical information, and practical clinical management is largely dependent on serial blood gas evaluation.

Blood Gases. When evaluating a blood gas result in an individual patient, one must take into consideration various factors such as the ambient atmosphere and pressure, and the position and age of the patient. For example, the normal findings in a healthy 20-year-old person standing up in Los Angeles differ notably from those in a relatively intact 80-year-old person lying down half way up Mount Whitney. In Los Angeles, an arterial oxygen partial pressure ($Pa\,O_2$) of less than 60 mm of mercury is probably abnormal; certainly a $Pa\,O_2$ less than 40 mm of mercury is indicative of a severe problem, which generally demands active alleviation. A hypoxic patient usually attempts to improve oxygenation by hyperventilating, thus causing a fall in the arterial partial pressure of carbon dioxide ($Pa\,CO_2$); if the $Pa\,CO_2$ increases, this indicates that severe respiratory insufficiency has developed. However, it is difficult to say which of the following patients is in the worse condition: Patient A with a $Pa\,O_2$ of 60 and a $Pa\,CO_2$ of 55, or Patient B with a $Pa\,O_2$ of 55 and a $Pa\,CO_2$ of 40 mm of mercury. Patient A may be in greater danger of hypoventilatory respiratory failure, such as often occurs in a patient with chronic airway disease in whom pneumonia develops and who gradually becomes exhausted, until apnea eventually occurs. However, Patient B who has more severe lung disease, with greater hypoxemia, nevertheless may have more staying power, with less danger of hypoventilatory respiratory arrest. Clinical judgment, rather than blood gas study results, is required when a prognosis is offered for such patients.

In practice, it is useful to consider two values in the assessment of a patient with ARDS. The first is the alveolar-arterial oxygen tension difference, (A-a) P_{O_2}, which is approximately equal to $140-(Pa\,O_2+Pa\,CO_2)$. For Patient A the (A-a) $P_{O_2}=140-(60+55)=25$, whereas for Patient B, (A-a) $P_{O_2}=140-(55+40)=45$. The pronounced (A-a) P_{O_2} in Patient B indicates the presence of more severe parenchymal disease which interferes with effective gas exchange in the alveoli. In contrast, in Patient A there may be relatively little interference with gas exchange, and the abnormal blood gases are largely attributable to hypoventilation.

The second measurement that can be evaluated is the venous admixture, and this can be determined as the shunt fraction fairly easily, particularly if the patient has an endotracheal tube or a tracheostomy in place. The patient must breathe 100 percent oxygen until equilibration occurs,

TABLE III-4.—*Physiologic Changes in ARDS*

Blood Gases	
$Pa\,O_2$	Decreased or normal
$P_{\bar{v}}O_2$	Decreased or normal
$Pa\,CO_2$	May be decreased, but increases with respiratory failure
(A-a) P_{O_2}	Increased
Shunt fraction	Increased
Lung Mechanics	
Breathing rate	Increased (often rapid and irregular)
Tidal volume (V_T)	Decreased, normal or increased
Vital capacity (VC)	Decreased or normal
Dead space/tidal volume (V_D/V_T)	Increased
Functional residual capacity (FRC)	Decreased
Expiratory reserve volume (ERV)	Decreased (may fall to zero)
Closing volume (CV)	Increased (may exceed FRC)
Forced expiratory volumes (FEV)	Decreased
Other	
Distribution of ventilation	Impaired
Diffusing capacity (DL_{CO})	Decreased
Diffusion/Alveolar volume (DL/VA)	Decreased
Compliance (C_L)	Decreased
Work of breathing	Increased
Inspiratory force	Decreased

$Pa\,O_2$ = arterial oxygen partial pressure
$P_{\bar{v}}O_2$ = mixed venous oxygen tension
$Pa\,CO_2$ = arterial partial pressure of carbon dioxide
(A-a)P_{O_2} = alveolar-arterial oxygen tension difference

which usually takes about 15 minutes, after which an arterial sample is taken. The graph illustrated in Figure III-3 allows a reasonable approximation of the shunt to be read off for measurements made at sea level. An increased shunt percentage is directly correlated with the severity of the lung disease.

A further measurement of value in patients

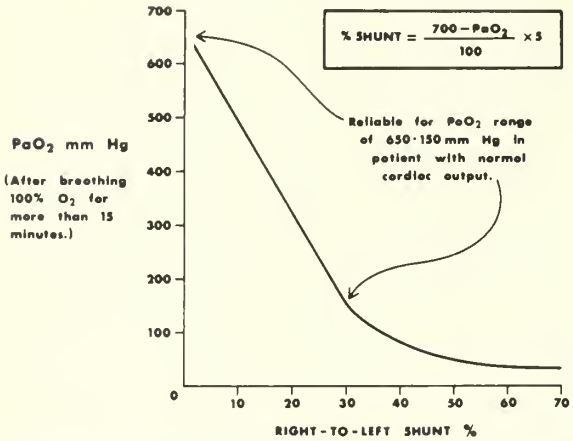

Figure III-3.—This diagram presents the conceptual basis for the estimation of the right-to-left shunt at sea level. (Reproduced by permission from Ayers LN, Whipp BJ, Ziment I: A Guide to the Interpretation of Pulmonary Function Tests. New York, Projects in Health, Inc., 1974.)

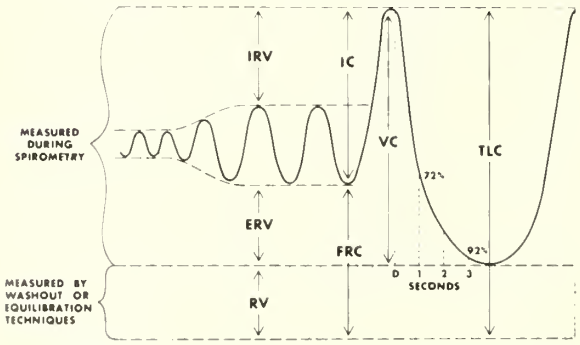

Figure III-4.—Spirogram showing volumes and capacities and forced vital capacity. In severe pneumonia, the total lung capacity (TLC) and vital capacity (VC) are reduced. The tidal volume may be decreased or may be increased. The inspiratory capacity (IC) and the inspiratory reserve volume (IRV) are usually reduced, while the expiratory reserve volume (ERV) and the functional residual capacity (FRC) are notably decreased. The residual volume (RV) is variably affected.

These measurements are not usually made at the bedside with the exception of the tidal volume and the vital capacity. Determination of TLC, RV and FRC can only be made in the laboratory.

Flow rates can be measured at the bedside; these are usually reduced in severe pneumonia. (Reproduced by permission from Ayers LN, Whipp BJ, Ziment I: A Guide to the Interpretation of Pulmonary Function Tests. New York, Projects in Health, Inc., 1974.)

with severe hypoxemia who require respiratory support is the mixed venous oxygen tension (P_VO_2).[45] Usually, blood taken from the right side of the heart has a P_VO_2 greater than 35 mm of mercury. If the value is less than this, the tissues are liable to suffer from hypoxic damage. It may be more important to maintain an adequate P_VO_2 rather than to strive for a supposedly adequate Pa O_2, and sometimes the two values do not correlate.[46] Therefore, high pressure gas flow provided by a ventilator may increase the Pa O_2, but by decreasing the cardiac output, it may result in a fall in P_VO_2, which implies a decrease in tissue oxygenation. If a patient is seriously ill with ARDS, a central venous catheter may have the added value of permitting monitoring P_VO_2.

Lung Mechanics. Simple bedside measurements can be made which will provide reliable enough indications of tidal volume, vital capacity and flow rates in patients who can cooperate. Other measurements which may be of value in patient management include the inspiratory force (which is determined by having the patient inspire through a tube linked to a manometer), and, in the case of an intubated patient, the dead space-tidal volume ratio (V_D/V_T).[47]

These values, which are routinely measured on most respiratory care units, can be correlated with the blood gas values and the clinical state to determine whether intubation and respiratory support is necessary, or to help determine whether respiratory support can be discontinued.[48]

Other Physiologic Abnormalities in ARDS

The hallmark of the acute respiratory distress syndrome in severe pneumonia and other parenchymal or interstitial lung diseases includes mismatching of ventilation and perfusion (V/Q abnormality), a decrease in pulmonary compliance (that is, a fall in the amount of gas entering the lung for a given change in transpulmonary pressure) and a reduction in functional residual capacity (FRC).[47]

The functional residual capacity is the volume of gas remaining in the lungs after a normal, unforced expiration (see Figure III-4). In obstructive airway disease, this amount is increased, whereas a decrease occurs with restrictive conditions such as obesity and lying supine or head down. In ARDS, all lung volumes may be decreased, and there is a pronounced reduction in FRC, which correlates with the decrease in Pa CO_2. The fall in FRC is mainly due to decrease in the

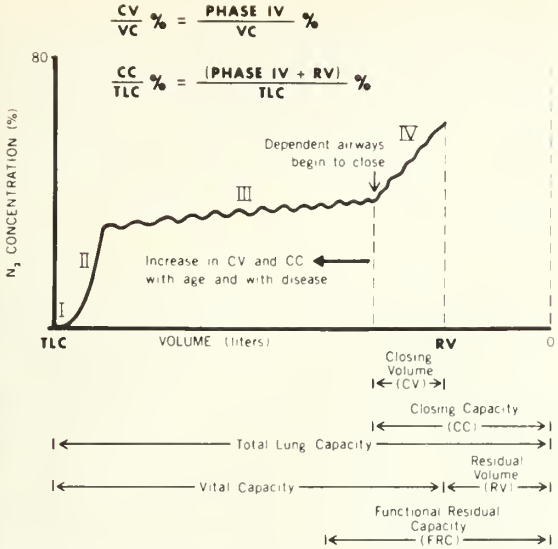

Figure III-5.—Closing volume and closing capacity. Characteristic changes in expired nitrogen concentration which occur during a vital capacity maneuver following an inhalation of 100 percent oxygen.

TLC = total lung capacity; IV = inspiratory volume; VC = vital capacity. (Reproduced by permission from Ayers LN, Whipp BJ, Ziment I: A Guide to the Interpretation of Pulmonary Function Tests. New York, Projects in Health, Inc., 1974.)

expiratory reserve volume (ERV), that is, the amount of gas that can be expelled by further effort after a normal expiration. A very dyspneic patient with severe pneumonia may utilize all his ERV, so that no further air can be forcibly exhaled after each expiration.

Damage to the small airways in pneumonia, with the associated mucosal swelling from interstitial inflammation and edema, results in early closing of these airways during expiration, particularly in the dependent lung regions. Since airway closure results in gas trapping, the closing volume and closing capacity are increased in ARDS (Figure III-5). Under such circumstances, atelectasis may occur, and this problem is increased by impaired surfactant production in severe lung infections.

Respiratory Management of Severe Pneumonia

Treatment of the Pathogen

Appropriate antimicrobic management is obviously essential. In some cases, aspiration of involved parenchyma using a transthoracic spinal needle allows early identification of the organism without unacceptable risk to the patient. In other cases, transtracheal aspiration, bronchoscopic suctioning or open or closed biopsy may be needed, if simple sputum examination is unsuccessful. The exact antibiotic or chemotherapeutic agent to be used depends on the clinical situation and microbiological data as discussed by Dr. Galpin.

TABLE III-5.—*Endotracheal Intubation*

A. Reasons for Intubating in Adult Respiratory Distress Syndrome
   1. To permit ventilation if patient becomes apneic.
   2. To facilitate delivery of oxygen if more than 60 percent is required.
   3. To permit suctioning and airway lavage if there is excessive mucus retention.
   4. To facilitate the delivery of constant humidity/aerosolization.
   5. To facilitate the delivery of other pharmacologic agents.
   6. To provide the advantages of respiratory support, e.g. high tidal volume, controlled minute ventilation, control of $Pa\,CO_2$, sighing, PEEP.
   7. To forestall aspiration.
   8. To permit adequate analgesia or sedation in an exhausted patient.
   9. To facilitate control of restless or uncooperative or struggling patient.
   10. To permit more accurate ventilatory control and monitoring, e.g. V_D/V_T isopleths can be employed if patient is on a volume respirator.

B. Alternatives to Intubation
   1. Frequent use of skillfully given IPPB, e.g. for ten minutes every hour.
   2. Appropriate use of postural drainage, chest percussion and other techniques in physical therapy.
   3. Emplacement of nasopharyngeal airway, to permit frequent endotracheal suctioning.
   4. Use of tight fitting pressure mask with high oxygen flow/IPPB; can be used in moderately uncooperative patient.
   5. External tank or cuirass respirator.
   6. Augmentation of respiration by use of a rocking bed.
   7. Stimulation of coughing by a Cofflator machine.
   8. Nursing patient in optimal position (e.g. head of bed elevated) to improve oxygenation.
   9. Tracheostomy (which is appropriate and preferable to nasotracheal or orotracheal intubation when prolonged respiratory support can be anticipated).
   10. Vigorous combination of several of above may obviate need for intubation.

$Pa\,CO_2$ = arterial partial pressure carbon dioxide
PEEP = positive end expiratory pressure
V_D/V_T = dead space/tidal volume
IPPB = intermittent positive pressure breathing

Oxygen Therapy

Dyspneic or hypoxemic patients require carefully controlled oxygen therapy. In less severe cases, oxygen given by nasal cannula suffices; for each 1 liter flow, about 3 percent oxygen is added to the room air, up to a maximum of about 45 percent, which is achieved with 8 to 10 liters of oxygen. In some patients an aerosol mask is preferable, since this provides the advantages of

humidity, and perhaps 50 to 55 percent oxygen can be delivered. If more oxygen is required to keep the Pa O_2 above 50 mm of mercury, the patient will probably require intubation, and will generally need respiratory support. Table III-5 lists the indications for intubation, and also enumerates alternatives to the use of an endotracheal tube.

There is a danger of producing oxygen toxicity if more than 60 percent oxygen is given for longer than 24 to 48 hours. If it is not possible to maintain a Pa O_2 of 50 with a fractional concentration of oxygen inspired gas (FIO_2) of 60 percent oxygen while on respiratory support, positive end-expiratory pressure (PEEP) may be required.[49] This maneuver results in an increase in the FRC, which may be accompanied by a pronounced rise in Pa O_2. However, there is a danger of PEEP causing a decrease in venous return resulting in a fall in cardiac output. The P_VO_2 may fall under such circumstances, and monitoring this indicator of oxygenation is of value in a very hypoxemic patient.[50]

Patients with severe viral pneumonia may remain dangerously hypoxemic with a Pa O_2 of less than 50 mm of mercury when receiving 70 percent oxygen, with appropriate tidal volumes and minute ventilation, and PEEP of 15 cm of water. Under such circumstances, the use of a membrane oxygenator using extracorporeal circulation should be considered as a possible lifesaving measure.[51] Hyperbaric oxygen therapy has not, as yet, been shown to be of practical value in the management of critically ill patients with ARDS.

Fluid Balance

The lungs in patients with severe pneumonia are heavy, and contain increased amounts of water. Improved oxygenation may result from positive pressure ventilation or from PEEP, in part because these maneuvers decrease the fluid content of the lungs by decreasing venous return and by discouraging exudation from the alveolar capillaries. Diuretic therapy may be of value, but great care is required to prevent adverse changes in fluid balance. The use of a central venous catheter and of pulmonary wedge-pressure measurements by a Swan-Ganz catheter can be extremely helpful. Respirator use often results in an increased secretion of antidiuretic hormone (ADH), which further compounds the difficulties of fluid balance management. Monitoring the measured cardiac output can also be of great help, particularly when using PEEP. If evidence of heart failure develops, cautious use of digoxin may be needed. Frequently, the toxic, hypoxic myocardium is susceptible to arrhythmias, and administration of various antiarrhythmia drugs may be necessary.

Corticosteroids

The role of these drugs in severe pneumonias is quite controversial. Use of steroids leads to increased problems with regard to containment of the infection and management of fluid balance. However, these drugs may have a beneficial effect on the damaged alveolar-capillary membrane, and may prevent or help treat complications of septic shock. Certainly, a patient whose condition is deteriorating while adequate antimicrobial drug therapy is being carried out may be regarded as suitable for a cautious trial of steroid therapy.

Respiratory Drugs

For most patients with severe pneumonia the benefit of bronchodilator therapy is required.[52] Intravenously given aminophylline is usually helpful, the appropriate dose being 5 mg per kg of body weight loading dose followed by 1 mg per kg of body weight per hour as a continuous drip, or the appropriate amount every six hours by bolus administration. Inhalational catecholamines may be given, as long as there is no adverse cardiac effect.

The abnormal secretions should be treated by mucokinetic agents[53] including aerosolized water, or a 2 to 7.5 percent solution of sodium bicarbonate. If the secretions are very viscous, 2 ml of a 20 percent solution of acetylcysteine diluted with an equal amount of sodium bicarbonate can be instilled or nebulized every 1 to 6 hours. A valuable agent is sodium iodide, given by continuous intravenous drip, with a total of 1 to 3 grams per 24 hours.

Some authorities give antibiotics, corticosteroids and other drugs by the inhalational route, but in general these drugs are ineffective or hazardous when given in this fashion.

Prognosis in Severe Pneumonia

The advent of respiratory care units allows intensive, sophisticated management of severe pneumonias. Undoubtedly skillful care results in improved rates of survival, but unfortunately many patients with severe pulmonary infections are elderly or debilitated, or have abnormal lung

architecture or impaired immunologic mechanisms. The presence of such adverse circumstances notably lowers the success of even the most skillful and sophisticated management, and clinical judgment is required to determine whether the complex and dangerous modalities involved in total respiratory care are justified for an individual patient with overwhelming pneumonia.

DR. OILL: Dr. Paul Selecky will now discuss two separate respiratory problems. The first is pulmonary hemorrhage secondary to earlier infection in the lung. The second is the processes that involve the neurogenic control of respiration and may manifest as alveolar hypoventilation.

The final speaker for this part of the symposium is Dr. Jerome Schofferman, who will address himself to the evaluation, pathophysiology and management of anaphylaxis.

Hypoventilation Syndrome and Pulmonary Hemorrhage

PAUL SELECKY, MD:* Various types of infectious disease emergencies can involve the respiratory system, most of these being the result of a primary infection of the lung by some pathogen. These are described elsewhere in this symposium. Two unique situations that may present to the emergency department should be mentioned separately. One special problem is the occurrence of an acute pulmonary hemorrhage secondary to an earlier infection in the lung. Another is the phenomenon of *alveolar hypoventilation* (hypoxemia and hypercapnia) secondary to a disturbance in the neurogenic control of breathing which is caused by some infectious process. In brief, the latter situation pertains to the patient who presents with dyspnea and abnormal arterial blood gas values despite normal findings on a roentgenogram of the chest.

Pulmonary Hemorrhage

Massive hemoptysis is a frightening event for both patient and physician. Even the slightest amount of blood in the expectorated sputum is of great concern. Physicians in the emergency department, however, usually do not get involved unless the amount of bleeding is significant. By definition, this has been categorized as hemoptysis that produces more than 600 ml blood in 24 hours.

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TABLE III-6.—*Management of Pulmonary Hemorrhage*

1. Protect airway: erect position, artificial airway.
2. Support vital functions: oxygen, transfusions.
3. Stop bleeding: airway care, treat any clotting disorder.
4. Identify bleeding site: chest roentgenogram, early bronchoscopy.
5. Thoracotomy for massive bleeding (greater than 600 ml/24 hrs).

The cause is most commonly the breakdown of lung tissue secondary to a chronic infectious process, such as bronchiectasis, pulmonary tuberculosis or fungal disease, and lung abscess.[54] Bronchogenic carcinoma can also be a cause of hemoptysis, but this usually does not cause a pulmonary hemorrhage, except occasionally terminally.

There is often difficulty in quantitating the amount of expectorated blood. The findings on a roentgenogram of the chest are not always helpful—a small abscess can be the cause of a large amount of bleeding, while grossly abnormal findings on a roentgenogram may represent a presently quiescent condition. The basic approach to the treatment of pulmonary hemorrhage, therefore, is to admit the patient to hospital and observe him closely.

Guidelines for the acute management of this problem are depicted in Table III-6. The basic tenets of protecting the airway and supporting vital functions are the keystone. In most patients endotracheal intubation is not needed, but clinical judgment must prevail. Blood in the airway can be very irritating, resulting in violent coughing, such that intubation can sometimes be quite beneficial for suctioning even though assisted ventilation may not be necessary. If progressive hypoventilation develops, however, a respirator should be employed. The other modalities of good respiratory care must also be utilized—bronchodilators, humidification and postural drainage. Chest percussion should most likely be avoided for fear of perpetuating the bleeding, although this has not been substantiated.

Recent reports in the surgical literature have supported early thoracotomy for the treatment of massive hemoptysis.[55,56] For this reason, bronchoscopy should be used early in the patient's course to try to identify the anatomic site of bleeding.[57] This applies to a patient with minimal hemoptysis as well, because it is generally unpredictable whether in such a patient a life-threatening hemorrhage may occur hours later. Bronchoscopy at that time is often unsuccessful

in locating the bleeding site because the blood is scattered throughout the tracheobronchial tree.

The mortality in patients with massive hemoptysis varies with the duration and intensity of the blood loss, but has been reported to exceed 75 percent when the bleeding of 600 ml occurred within 16 hours.[55,56] With early lung resection in these patients, the mortality decreased to 23 percent, indicating that nonoperative management was inadequate. Generally, patients with hemoptysis will improve with basic airway care alone. The occasional patient with brisk bleeding, however, may profit from early thoracotomy, provided that the anatomic bleeding site has been identified, and that the patient has adequate pulmonary reserve to tolerate lung resection.

Alveolar Hypoventilation

Alveolar hypoventilation is diagnosed by laboratory evidence of disordered gas exchange, specifically, hypercapnia and hypoxemia by arterial blood gas values while breathing room air. This can be the result of a multiplicity of disorders, including primary lung diseases and disorders of the control of breathing. The latter refers to problems involving the neural pathway from the respiratory center in the central nervous system (CNS), down the nerve roots, to and including the respiratory muscles themselves. It is this less common cause of alveolar hypoventilation that I will focus on.

Problems with the control of breathing from infectious causes include any infection that can result in severe CNS depression—for example, encephalitis, meningitis, brain abscess or a generalized sepsis. The group of diseases that are described in this section present in yet another way. Briefly, the typical presentation is that of a patient who enters the emergency department with complaint of dyspnea, is unable to inspire effectively, or perhaps aspirates every time he tries to swallow. He is generally weak and quite frightened. He may have noticed some blurred vision or diplopia or perhaps some distal paresthesias. On examination the patient is found to be mentally alert, but has diffuse motor weakness and nasal speech, and is perhaps somewhat ataxic. Findings on studies of arterial blood gases show hypercapnia and hypoxemia, but on examination of the lungs and on a roentgenogram of the chest no abnormalities are seen. By definition, the patient has alveolar hypoventilation. The problem now is to consider what infectious disease states must be included in the differential diagnosis of this presentation—that is, an alert patient in whom there are normal findings on a chest examination and who is perhaps diffusely weak and is hypercapneic and hypoxemic.

TABLE III-7.—*Infectious Causes of Hypoventilation Secondary to Neuromuscular Dysfunction*

Polyneuritis
Guillain-Barré syndrome
Acute poliomyelitis
Rabies
Neurotoxin
Tetanus
Botulism
Tick paralysis
Diphtheria
Neuromuscular blockade
Complications of antibiotic use

Table III-7 describes three categories of infections that can present as alveolar hypoventilation. These include the neuromuscular weakness that can occur as the result of (1) a polyneuritis or similar disturbance (Guillain-Barré syndrome, acute poliomyelitis and rabies), (2) the effects of a neurotoxin either from direct infection of an organism (tetanus, tick paralysis, diphtheria) or ingestion of toxin-contaminated foods (botulism), or (3) a neuromuscular blockade that can occur with the use of certain antibiotics.

Polyneuritis

Guillain-Barré syndrome. This is a clinical entity that has no identifiable cause, although it has commonly been seen during the convalescent phase of an upper respiratory infection or gastroenteritis, suggesting a viral origin. Characteristically, the patient presents with a symmetrical muscle weakness and tenderness that starts distally in the legs and can ascend in a progressive manner—in other words, ascending paralysis. In many patients cranial nerve involvement may also develop. Distal paresthesias have been described, as well as stocking-glove sensory losses.[58] The patient is afebrile; studies of spinal fluid show an elevated protein level with very few cells (predominantly mononuclear).

Most of such patients are moderately incapacitated by weakness, but as many as 15 to 40 percent may progress into respiratory failure and possible death unless full respirator support is carried out.[59,60] The physician's immediate responsibility is to follow the patient closely to avert such respiratory failure. The appropriate measurements and treatment of this hypoventila-

tion will be discussed below. There is no specific treatment for this disorder. It is generally a self-limited disease, but may have a prolonged recovery period, lasting six months to two years.

Acute poliomyelitis. This is a generalized viral illness which typically leads to destruction of the motor cells in the spinal cord and brain stem with subsequent nerve degeneration and flaccid paralysis. Before 1956 there were as many as 50,000 cases each year.[61] The advent of orally given polio vaccine has fortunately made this illness a rarity; less than 50 cases are now being recorded a year.[62] Despite public health efforts, occasionally a child escapes adequate immunization and may present with the disease. Initial symptoms include a flu-like illness with fever for 2 to 3 days, followed by increasing headache, muscle soreness and stiff neck. This may then resolve, but in a small group may be followed several days later by a flaccid and asymmetrical paralysis, commonly involving the lower extremities and trunk; in about 15 percent of patients bulbar palsy develops. Spinal fluid examination results show a lymphocytosis but normal protein level, in contrast to Guillain-Barré syndrome. Diagnosis is generally made on clinical evidence, but can be confirmed by a four-fold rise in neutralizing antibody titer. Treatment is generally supportive. Evidence of respiratory difficulty requires vigorous treatment; mortality in such patients can reach 50 percent.[61]

Rabies. This disease is included in this series of respiratory emergencies, although the primary role of the physician lies in preventing the disease long before any respiratory problems may arise. This results from the fact that the encephalitis caused by this neurotropic virus is universally fatal (with one exception[63]) unless prophylactic treatment is administered immediately upon suspected exposure to the virus. The disease is acquired by contact with the saliva of an infected animal either by bite or lick. The incubation period lasts about two weeks, but has been described as lasting one year. The active infection presents as headache, fever, nausea and vomiting, paresthesias, muscle spasms and seizures that proceed to death in 5 to 14 days. The severity depends on the dose of the inoculum and its proximity to the CNS. Once established in the nerve root, fatal CNS involvement is unavoidable.

The only successful treatment is to inoculate the patient with antiserum and vaccine at the time of exposure. Approximately 600,000 people are bitten each year in the United States by animals that potentially are infected. About 35,000 are treated with the vaccine; 3,000 also are given the equine antiserum (and in about 45 percent of these serum sickness develops).[64] The success of this therapy is noted by the low incidence of rabies deaths (two per year).[62]

Treatment must be started immediately, ideally within 24 hours of exposure.[65] Each physician must, therefore, be acquainted with the indications and methods of treatment, which have been outlined by the World Health Organization.[66-68] In brief, any bite by a wild skunk, fox, raccoon or bat requires immediate treatment with both rabies vaccine and antiserum. Bites by domestic animals must be evaluated individually. The arguments against the use of equine antiserum because of the fear of serum sickness are now resolved with the availability of human rabies immune globulin.[64] Suggested treatment regimens include: local wound care, active immunization with duck embryo vaccine (1 ml given subcutaneously daily for 21 days, plus two boosters at 10 and 20 days after last daily dose), and human antiserum injected in the bite and systemically (15 to 40 units per kg of body weight given intramuscularly).

Neurotoxin

Tetanus. This is an anaerobic Gram-positive bacillus infection due to Clostridium tetani resulting in neuromuscular dysfunction secondary to the release of a neurotoxin. It is an uncommon problem since the advent of tetanus immunization (an average of 175 cases each year)[62] but can occasionally be seen in heroin addicts or in non-immunized persons. The disease occurs as the result of bacterial contamination of an injury or wound which has an appropriate anaerobic condition (for example, tissue necrosis), allowing the spore forms to develop into the toxin-producing vegetative forms. Corrosive metals, soil and animal feces are common sources for Clostridium tetani inoculation. Despite partial healing of the initial injury, the patient presents some 6 to 14 days later with signs of neuromuscular hyperirritability-hyperreflexia, muscle spasms (trismus, dysphagia, risus sardonicus) and dysautonomia (labile hypertension, sweating, tachycardia). Depending on the amount of circulating neurotoxin, this may ultimately progress to opisthotonos, seizures and death due to asphyxia. These symptoms are the result of synaptic inhibition by the

blood-borne toxin as it becomes bound to nerve tissue. Diagnosis is based largely on clinical evidence; the organism is very difficult to grow in culture.[69]

Treatment must be vigorous—the mortality can exceed 50 percent in severely infected patients especially at the extremes of age.[61] Public Health data record an average of 100 deaths a year for the nation.[62] Airway care is vitally important because of the laryngeal and chest wall tetanic spasms as well as the aspiration of secretions that can occur. Indications for tracheostomy and respirator support will be discussed below. Immediate treatment of the infection should follow these guidelines:[70]

- immediate passive immunization with antitoxin (human tetanus immune globulin, 6,000 to 10,000 units given intramuscularly and into the wound site);
- antibiotic therapy with intravenously given penicillin (5 to 10 million units per day) or tetracycline (500 mg given intravenously every six hours);
- wound debridement one to two hours *after* passive immunization has been completed;
- active immunization with alum-precipitated tetanus toxoid (0.5 ml given intramuscularly initially and again in six weeks and six months) following recovery;
- avoid repetitive intramuscular or subcutaneous injection which may precipitate muscle spasms due to the pronounced neuromuscular irritability.

Subsequent treatment of the muscle spasms has been achieved with various relaxants, including diazepam, chlorpromazine and occasionally curare.

Prevention has been the mainstay in decreasing the incidence of tetanus. If there is any doubt concerning the patient's immunization status at the time of a crush injury, recommended prophylactic treatment includes administration of: human tetanus antitoxin (250 to 500 units given intramuscularly), tetanus toxoid booster (0.5 ml given intramuscularly) and penicillin or tetracycline.[69]

Botulism. This is an uncommon syndrome with less than 50 cases being reported yearly.[62-71] The classical disease is not true infection, but rather a food poisoning that results from ingesting improperly preserved (and uncooked) vegetables, meat and fish that are contaminated with Clostridium botulinum (types A, B, E). However, occasionally an injury or wound may harbor the organism and result in the same clinical entity. The neurotoxin produced by the growth of this organism in food is readily absorbed and is transported to the myoneural junction where it acts to decrease the release of acetylcholine. The result is diffuse weakness in both smooth and striated muscles. About 12 to 48 hours after ingestion, depending on the dose of toxin received, the patient may complain of nausea and vomiting, diplopia, dysphagia and nasal speech. On examination a diffuse weakness in the trunk and all extremities, as well as ptosis and extraocular palsies is found. A distinguishing feature is the smooth muscle involvement, often presenting as dilated pupils, intestinal ileus and urinary retention. With profound paralysis, respiratory failure and coma may occur. Mentation is intact and there is no sensory involvement. (See Addendum.)

Diagnosis is made from findings on the clinical examination and the history of ingesting rancid-tasting and uncooked preserved food (the toxin is heat-labile and easily destroyed by heat). Analysis of the contaminated food and patient's serum for presence of toxin should be done for confirmation of diagnosis. Anaerobic culture of wounds is essential. Treatment consists of supportive measures plus administration of trivalent (ABE) botulinus antitoxin (20,000 to 40,000 units given intravenously) for symptomatic patients.[72] Despite comparable exposure, such as several members of a family eating the same meal, in less than half the patients will symptoms develop. All should receive a gastrointestinal purge. Careful observation for respiratory insufficiency is mandatory and preparation for early tracheostomy is crucial. Mortality from respiratory failure can be as high as 30 to 50 percent.[72]

Tick paralysis. Another disease-state that can present as diffuse weakness occurs as the result of a neurotoxin found in tick saliva. The patient is bitten by a wood or dog tick while hiking or camping; the tick then attaches itself to the skin for 5 to 7 days before symptoms develop. Clinically, the patient presents with a lower extremity weakness that can ascend to produce a diffuse flaccid paralysis. Results of sensory examination and spinal fluid studies are normal, in contrast to Guillain-Barré syndrome. Diagnosis is made by finding the tick imbedded in the skin, often on the scalp. Removal is usually followed by complete recovery in 24 hours. If unrecognized and un-

treated, mortality can range as high as 10 percent.[73] Physician awareness, therefore, is the chief link in determining the outcome of this totally reversible disease.

Diphtheria. This is a relatively rare disease which traditionally presents as a febrile, mild pharyngitis that causes the formation of a gray pseudomembrane on the pharynx. The more common cause of respiratory difficulty in this disease is upper airway obstruction that can occur from the pharyngeal web, and that aspect of the disease has already been discussed. It is included in this series because of the circulating neurotoxin that can be produced by the organism (Corynebacterium diphtheriae), causing a distal symmetrical weakness. Intercostal muscles and the diaphragm may also be involved, resulting in respiratory failure.

In most patients the neurotoxin is released only in the throat, but in 6 to 20 percent the diffuse polyneuritis may also develop.[61] The pharyngeal sensory loss can progress to include the cranial nerves in 5 to 12 days, followed by ciliary muscle paralysis and blurred vision by the end of the third week. Diffuse weakness can occur as late as two months after the initial infection. Active immunization procedures have fortunately made the disease uncommon (an average of 200 cases a year).[62] Occasional major outbreaks, however, continue to occur.[74] Treatment is generally supportive. Antibiotics (penicillin, tetracycline, erythromycin) and equine diphtheria antitoxin are administered for the pharyngeal stage. Antitoxin is ineffective for the treatment of the diffuse weakness because the neurotoxin has already become bound to the nerve. The period of recovery may be quite prolonged. The outcome is largely dependent on the quality of the respiratory support, although cardiac involvement with the toxin portends a poor prognosis. National mortality figures show an average of 20 to 40 deaths per year.[62]

Neuromuscular Blockade

Several antibiotics have been shown to be capable of producing significant neuromuscular blockade. The effects can vary from a mild weakness to a diffuse myasthenic-like paralysis with apnea and death. Perioral paresthesias, diplopia, ptosis and dysphagia, as well as smooth muscle effects (ileus), have also been described. The antibiotics in which this has been reported are listed in Table III-8. These are basically two groups of antibiotics: (1) *aminoglycosides* which produce a competitive blockade at the motor endplate that can be reversed with neostigmine or calcium and (2) the *polymyxin* group (B, E) which establish a noncompetitive blockade and cannot be eliminated with neostigmine (but are reversible with calcium). Other antibiotics have been associated with neuromuscular weakness (tetracycline, sulfonamides), but respiratory paralysis has not been described.[75]

TABLE III-8.—*Antibiotics That Can Cause Muscle Weakness and Hypoventilation Secondary to Neuromuscular Blockade*

Aminoglycosides
Gentamicin
Kanamycin
Dihydro/Streptomycin
Neomycin
Viomycin
Polymyxins
Polymyxin B
Polymyxin E (colistimethate)
Miscellaneous
Tetracyclines
Sulfonamides

Among the aminoglycosides, physicians are more likely to observe this complication with gentamicin because of its more common use,[76] although it can also be seen with streptomycin,[77] neomycin,[78] kanamycin[79] and viomycin.[80] The myasthenic-like effects of the polymyxin group also have been well described.[81]

The blockade caused by both groups of drugs is not dose-related and as such has occurred after only one dose, as well as after 45 days of therapy. Similarly, it can cause sudden apnea within one hour after drug administration or as long as 26 hours later.[81] The effects can take many forms, although a typical reaction might begin with dysphagia an hour after the drug is administered, followed by perioral paresthesias, diplopia and progressive dyspnea. Within 90 minutes the patient can be totally apneic. In a milder form, it can be difficult to distinguish these clinical features from myasthenia gravis or the Eaton-Lambert syndrome. Findings of an electromyogram are occasionally helpful.

Various experiences with this type of antibiotic-induced neuromuscular blockade have indicated that certain clinical factors might have predisposed the blockade, such as the additive effects of using several of these drugs in the same patient. Other factors included the antecedent existence of renal failure, hypocalcemia, other neuromuscular

TABLE III-9.—*Differential Diagnostic Features of Infectious Causes of Neuromuscular (NM) Weakness*

Disease	*Motor Weakness*	*Sensory*	*Other*
Guillain-Barré ..	Distal, symmetrical; can be bulbar	Paresthesias; ↑ proprioception, ↓ touch	↑ CSF protein; dysautonomia
Poliomyelitis ...	Asymmetrical	Normal	↑ CSF cells; fever
Botulism	Diffuse, symmetrical; cranial nerve; ileus	Normal	History of food ingestion, vomiting
Tick paralysis ..	Distal, symmetrical, ataxia	Normal	CSF normal; tick bite
Diphtheria	Distal, symmetrical; cranial nerve	Reduced touch/pain/proprioception	History of pharyngitis with web
NM blockade ...	Diffuse; cranial nerve; ileus	Paresthesias	History of drug exposure

CSF = cerebrospinal fluid

disorders (myasthenia gravis) or the administration of the drug onto a serosal surface (sinus irrigation, peritoneal lavage).[76,82] When one of these drugs must be used under such circumstances, the patients should be observed closely with repeated tests of muscle strength, much as a patient with Guillain-Barré syndrome is monitored, in order to avoid sudden respiratory embarrassment.

Supportive management of this syndrome is vital; on occasion, the blockade can be reversed. Paralysis secondary to the aminoglycosides has improved after the administration of calcium gluconate (25 grams given intravenously) or neostigmine (0.5 to 2 mg given intramuscularly or slowly intravenously; total dose less than 5 mg).[61,78,79] Unpleasant side effects of the neostigmine may require pretreatment with atropine.

The effects of polymyxin should be treated with intravenously given calcium only; neostigmine is ineffective and in fact may potentiate the blockade.[81] These antidotes are helpful but often do not obviate the need for respirator support.

Reviewing these many disease states shows that the neuromuscular weakness and respiratory paralysis can present in a similar manner. Treatment at times must be very specific, such that precise diagnosis is important. The clinical history will often be the greatest help, for example, ingesting rancid food, use of suspected antibiotic, recent camping trip. Other helpful differential features are described in Table III-9.

Respiratory Support

The treatment of respiratory failure has been well described by many authors[83,84] and therefore there will be no attempt to discuss it in depth here. The basic points of good respiratory care, however, should be emphasized. These include: (1) establishing a patent airway, (2) oxygen therapy and (3) determining the need for assisted ventilation, that is, respirator support.

Airway Care

The foundation of adequate support for patients with respiratory difficulty is to ensure a good airway. Many times this can be accomplished with proper positioning of the patient, or with the use of an oral airway to keep the tongue forward or a nasopharyngeal tube.[85] When this is not possible, or if the patient continues to aspirate saliva, an endotracheal tube should be passed under direct vision. The patient can then be supported with proper airway humidification and suctioning for periods of 3 to 7 days without serious sequelae.[86,87] Many of the symptoms of the diseases described here can improve or completely resolve during this interval, allowing the physician to extubate the patient.

Tetanus should be mentioned separately because of the laryngeal spasms that can occur. If these cause persistent respiratory insufficiency, a tracheostomy should be carried out. In other diseases, a tracheostomy might not be necessary unless an artificial airway is required for more prolonged periods. Meticulous tracheostomy care is then mandatory to avoid serious complications.[88]

Oxygen Therapy

Hypoxemia is a necessary part of alveolar hypoventilation, but might not be so severe as to cause significant dysfunction. Supplemental oxygen is easily administered, but a physician should have specific goals in mind, such as to supply the amount of oxygen necessary to maintain a $Pa\,O_2$ of 60 to 80 mm of mercury. A higher $Pa\,O_2$ is unnecessary, especially if it runs the risk of oxygen toxicity secondary to high inspired oxygen concentrations (greater than 50 percent).

Assisted Ventilation

It is often difficult to assess whether a patient should be intubated and placed on a respirator. This is especially troublesome in a patient with neuromuscular weakness, for example, with Guillain-Barré syndrome, in whom there might be moderate respiratory impairment, but in whom reasonable arterial blood gas values are still being maintained. Respiratory efforts are often at a high energy cost in such a patient, in which case ventilatory assistance would be quite helpful. At the same time, however, intubation and the use of respirators can carry a significant morbidity.[86,89,90]

The solution for this dilemma lies in making repeated physiologic measurements to assess the need for respiratory assistance. Some basic guidelines are listed in Table III-10. It is especially helpful to make frequent measurements of vital capacity. A trend of progressively lower vital capacity volumes is more helpful in indicating the need for respirator support than waiting for the rock-bottom vital capacity of 10 ml per kg of body weight. This measurement requires a conscious, vigorous effort by the patient, such that both muscular strength and patient cooperation are assessed. Other additive features such as increased airway secretions or cardiac arrhythmias increase the need for respirator support.

As the condition of the patient improves with some return of muscular strength, similar guidelines can be used to decide when to discontinue the respirator and remove the tracheostomy.[91,92] In brief, it is wise to gradually wean the patient from the respirator by allowing him to breath spontaneously for progressively longer periods, returning to the respirator in the interim. When he becomes safely independent from the respirator for 24 hours, it is likely that the tracheostomy can be removed.[88]

TABLE III-10.—*Clinical Indications for Respirator Support*

1. Vital capacity less than 10 ml/kg
2. Pa CO_2 greater than 50 mm Hg and rising (pH less than 7.25)
3. Oxygenation ratio (Pa O_2/% inspired O_2) less than 1.5
4. Clinical factors:
   - Respiratory rate greater than 40/min
   - Copious secretions
   - Hypotension; malignant arrhythmias
   - Mental obtundation

Pa CO_2 = arterial partial pressure carbon dioxide
Pa O_2 = arterial partial pressure oxygen

Anaphylaxis

JEROME SCHOFFERMAN, MD:* The treatment of many infectious disease problems includes the use of antibiotics. As always, we must be prepared to recognize and treat any side effects or complications that might arise from the therapy itself. The use of antibiotics is no exception. Certain antibiotic-induced problems are specific for that particular drug but one symptom complex, anaphylaxis, might be seen after the administration of any antibiotic. The list of agents that have caused anaphylaxis is quite long and includes many antibiotics, insect stings, snake bites, horse serum, contrast media, dextran, insulin, local anesthetics, certain foods and many, many more.

In the following discussion, I would like to reacquaint you with the signs and symptoms of the anaphylactic syndrome, the pathophysiology and the various treatment modalities available.

At the outset it may be prudent to repeat a warning. It is important to take careful history from each patient to whom you might administer any drug. Be alert for past adverse reactions and try to elicit the details of the reaction. Many patients believe they are allergic to a drug because they experienced nausea or diarrhea after taking it. Play it safe, however. An ounce of prevention is worth a pound of epinephrine.

It is clinically useful to consider anaphylaxis as a symptom complex that occurs within minutes to hours after exposure to an antigen in a suitably immunized host.[93] The symptoms are due entirely to the actions of the chemical mediators released during the reaction on various target organs[94] (see Table III-11). The particular end organ response will vary from one person to the next. In some patients, subjective symptoms may herald the onset of the entire syndrome before objective signs appear. A patient may just describe a feeling that "something is wrong." Others might relate a feeling of fright or a feeling of retrosternal tightness. Itching in or around the eyes, the throat or the ears may be described. We have seen several patients in whom the initial symptom was a feeling of overall warmth, soon followed by widespread itching and finally by hypotension or bronchospasm. At times dyspnea, stridor, hoarseness or a "lump" in the throat due to upper airway edema may be the initial problem, as might dizziness or faint secondary to hypotension.[94]

The symptom complex of anaphylaxis has been

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TABLE III-11—*The Symptom Complex of Anaphylaxis**

System and Reaction	*Symptoms*	*Signs*
Respiratory tract		
Rhinitis	Nasal congestion and itching	Mucosal edema
Laryngeal edema	Dyspnea	Laryngeal stridor; edema of cords
Bronchospasm	Cough; wheezing; sensation of retrosternal oppression	Cough; wheezing; rales; respiratory distress; tachypnea
Cardiovascular system		
Hypotension	Syncope; feeling of faintness	Hypotension; tachycardia
Arrhythmia	.....	Electrocardiographic changes: Nonspecific S-T segment and T-wave change; nodal rhythm; atrial fibrillation
Cardiac arrest	.....	Absent pulse; electrocardiographic change: Asystole; ventricular fibrillation
Skin		
Urticaria	Pruritus; hives	Typical urticarial lesion
Angioedema	Nonpruritic swelling of an extremity, perioral or periorbital region	Edema frequently asymmetrical
Gastrointestinal system		
.....	Nausea; vomiting; abdominal pain; diarrhea	.....
Eye		
Conjunctivitis	Ocular itching; lacrimation	Conjunctival inflammation

*From: Kelly JF, Patterson R: Anaphylaxis: Course, mechanisms and treatment. JAMA 227:1431-1436, Mar 25, 1975, Copyright 1974, American Medical Association.

clearly summarized by Kelly and Patterson.[93] The skin is often the first organ involved. Diffuse erythema, a feeling of generalized warmth, itching, urticaria or angioedema may be present singly or in combination. The urticarial lesions can be local or generalized and are usually quite pruritic. Moreover, coalescence of the lesions forming giant hives has been reported.[94] Angioedema may involve the face or extremities in an asymmetric fashion but if soft palate, epiglottis, larynx or trachea are involved, life-threatening upper airway obstruction (UAO) may ensue.

Eye involvement with tearing, itching and redness is not uncommon. This conjunctivitis is rarely serious but could be a warning of subsequent, more ominous physiologic sequelae.

Gastrointestinal complaints might include nausea, vomiting, abdominal pain or diarrhea which is rarely bloody. Again, these manifestations are usually not serious.

The life-threatening manifestations of the anaphylactic syndrome involve the respiratory tract or the cardiovascular system, or both. Rhinitis might be an early symptom and is usually of little consequence. UAO is the most feared problem. It can involve many areas of the upper airways and develop quite suddenly. The symptoms have been previously mentioned. Physical findings include inspiratory stridor, a prolonged inspiratory phase of respiration or pronounced retraction of accessory muscles of respiration. Simple direct visualization of the palate and uvula may show the pronounced edema. Bronchospasm is more commonly seen. Cough, wheezing or a feeling of tightness behind the sternum are typical complaints. Expiratory wheezes will be present but if bronchospasm is severe and air flow limited, wheezes may be minimal or absent.

Cardiovascular manifestations can involve the heart or peripheral vascular system. Hypotension, when present, seems to be due to a reduction in effective plasma volume secondary to escape of fluid from the intravascular compartment and a resultant decrease in cardiac output.[95] Hypotension may also be a sequela of profound hypoxia. Various electrocardiographic abnormalities have been described including atrial fibrillation, other supraventricular arrhythmias, transient left bundle branch block, ventricular fibrillation and even asystole.[95-97] ST segment and T wave abnormalities can mimic myocardial ischemia or injury[95,96] and at times elevations of cardiac enzymes have been present.[96]

Although the signs or symptoms of the anaphylactic syndrome may be characteristic, certain other disease processes should be considered in

the differential diagnosis. The common fainting episodes (vasovagal reaction) secondary to any painful injection and the pseudoanaphylactic syndrome following inadvertent intravenous administration of procaine penicillin[98] have to be considered. Certain viral illnesses produce a rash which may have been initially overlooked, but becomes clinically evident coincidentally following administration of a drug or antibiotic. Some drugs produce toxic erythema. Phenothiazine injections can cause hypotension. Several drugs may precipitate wheezing in patients with the "aspirin sensitivity syndrome."[99]

The period of time from exposure to the antigen to onset of symptoms is variable and depends on the individual patient, route of administration and dosage. After oral ingestion of antigen, symptoms might occur after only five minutes instead of several hours later, as one might anticipate. Generally, patients present with complaints soon after parenteral exposure but again the time course is variable. A general rule might be to observe all patients who have received medications in an outpatient setting for 30 to 60 minutes before discharge.

The duration of symptoms is also unpredictable. Reactions may resolve almost immediately with therapy but at times can linger for 24 to 48 hours despite seemingly adequate treatment. In addition, attacks that appear to have subsided do recrudesce. Consequently, patients who suffer severe systemic reactions should be admitted to the hospital and observed for at least 12 to 24 hours after all signs and symptoms have cleared before discharge. Careful judgment is necessary for patients with less severe attacks. Mild reactions may be harbingers of more life-threatening events and, therefore, all patients should be observed for several hours. Before discharge, a physician or nurse must meticulously explain to the patient the signs and symptoms of the entire anaphylactic syndrome. The patient should be instructed to return to an emergency facility immediately if any occur. It is also wise to prescribe sufficient oral medications (see below) to be taken during the following 24 to 48 hours.

In order to logically approach the therapy of anaphylaxis, we must briefly review the pathophysiology.[93,94] The first stage of an anaphylactic reaction occurs at some time, perhaps forgotten or unknown, when the host is originally sensitized to an antigen. Specific antibodies (IgE) are formed which attach to the surface of mast cells and basophils. Reexposure to the foreign substance results in antigen bridging of two IgE molecules on the cell surface with resultant membrane changes and release of the pharmacologic mediators.[94]

Histamine is the chemical mediator most closely linked to human anaphylaxis. It is found in mast cells, basophils, platelets and the parietal region of the stomach.[94] In man, histamine causes bronchial constriction[93] which may be a vagal reflex rather than a direct action on smooth muscle.[94] Intravenous administration of histamine does cause increased capillary permeability, vasodilation, hypotension, headache and flushing.[93,94]

Slowly reacting substance of anaphylaxis (SRS-A) is also thought to play a role in human anaphylaxis.[93,94] It too causes contraction of human bronchial smooth muscle and at least *in vitro* may potentiate the smooth muscle actions of histamine.

Bradykinin, serotonin and prostaglandins have all been implicated in the animal model of anaphylaxis but the role of these substances in the human syndrome is not fully clarified. The role of eosinophil chemotactic factor (ECF-A) is also not completely understood.[94]

It is important to note that the immunological release of chemical mediators is closely linked to levels of cellular cyclic adenosine monophosphate (c-AMP).[93] However, other pathways for mediator release are suggested as well. Increased levels of c-AMP tend to decrease release of histamine and SRS-A after antigen challenge while decreased c-AMP levels favor mediator release. Drugs such as the beta-agonists increase c-AMP levels and thereby decrease mediator release and alpha-agonists tend to do the opposite. These important actions lead us into a discussion of the therapy of anaphylaxis.

Initial treatment for this syndrome must be directed toward life-threatening manifestations. Immediate attention to the airway is most essential. Upper airway obstruction must be dealt with promptly. Early therapy with epinephrine may improve upper airway edema but if obstruction progresses, tracheostomy should be strongly considered. It is often difficult to carry out endotracheal intubation in this situation. In fact, repeated attempts at endotracheal intubation may further aggravate airway obstruction. Local application of epinephrine or steroids does not appear to be helpful. Oxygen should be used as necessary. It is essential to evaluate the condi-

tion of a patient closely both clinically and with arterial blood gas analysis to ensure adequate ventilation and perfusion.

Hypotension commonly responds to fluid infusion or elevation of the legs, or both. Use of epinephrine is definitely indicated and the response may at times be dramatic. Repeated doses may be needed. Alpha adrenergic drugs should be avoided if possible. Rarely, isoproterenol may be indicated.

From these initial recommendations, it is clear that epinephrine is the cornerstone of therapy and remains the drug of choice to treat all aspects of the anaphylactic syndrome. Route, dosage and frequency of administration must be judged according to the clinical setting. Epinephrine acts at two levels. It interferes with further mediator release and antagonizes the effect of the mediators on target organs. For most patients, 0.3 to 0.5 ml of 1:1,000 epinephrine is recommended. Subcutaneous injection is effective if the patient is not hypotensive or notably vasoconstricted. However, if absorption from a subcutaneous site is inadequate or questionable, deep intramuscular injection is preferred. With hypotension or shock, 0.1 ml of epinephrine diluted in 10 ml of saline solution should be administered intravenously.

The antihistamines are also useful. Diphenhydramine is used most often and the route is dependent on the clinical features. Antihistamines act as competitive inhibitors of histamine at the target organ[93] and do not interfere with histamine release. A dose of 50 to 80 mg (maximum of 5 mg per kg of body weight per 24 hours) may be given every six hours orally or intravenously as indicated.[100] If moderate or severe bronchospasm is present, use of antihistamines may be dangerous because of their sedative properties.

Aminophylline should be added to epinephrine when moderate or severe bronchospasm is present. As in the treatment of any acute asthmatic attack, a loading dose of 375 mg[101] or 5.6 mg per kg of body weight[102,103] may be given over 7 to 10 minutes intravenously and followed by continuous drip therapy of 0.9 mg per kg of body weight per hour[101] or intermittent boluses of 250 mg every four to six hours. Oral bronchodilators are also useful for mild bronchospasm or for temporary maintenance therapy after the initial attack has subsided.

Corticosteroids are not useful for the acute situation. They are usually reserved for severe attacks unresponsive to the above modes of therapy. Dosage has been arbitrary, a dose of 60 to 125 mg of methylprednisolone intravenously every six hours appears efficacious.

Local therapy for anaphylaxis is directed toward prevention of further absorption of the antigen, and must be instituted early for maximum benefit. One such local measure would be placing a constricting band proximal to the site of antigen inoculation, such as an insect sting or injection. Alternatively, or in addition, local instillation of epinephrine might be beneficial.

Patients must also be carefully warned to avoid the suspected antigen in the future. Consultation with an allergist to consider skin testing and desensitization may be warranted. Carrying of medical warning jewelry or wallet card is a useful and worthwhile practice.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Polycillin®, Omnipen®, Totacillin®, Amcil®, Penbretin®, Principen®	*ampicillin*
Kantrex®	*kanamycin*
Chloromycetin®	*chloramphenicol*
Cleocin®	*clindamycin*
E-mycin®, Erythrocin®, Kesso-mycin®, Ilotycin®, Robimycin®, Pediamycin®	*erythromycin*
Vancocin®	*vancomycin*
Keflin®	*cephalothin*
Garamycin®	*gentamicin*
Nebcin®	*tobramycin*
Amikacin®	*BB-K8*
Geopen®	*carbenicillin*
Pentamidine	*pentamidine isethionate*
Symmetrel®	*amantadine HCl*
Digoxin®, Lanoxin®, Davoxin®	*digoxin*
Aminophylline	*aminophylline*
Mucomyst®	*acetylcysteine*
Achromycin®, Panmycin®, Tetracyn®	*tetracycline HCl*
Valium®	*diazepam*
Thorazine®	*chlorpromazine*
Hyper-tet®	*human tetanus immune globulin*
Polymyxin B sulfate	*polymyxin B sulfate*
Mycifradin® Sulfate	*neomycin*
Viocin® Sulfate	*viomycin sulfate*
Prostigmine®	*neostigmine*
Nycillin®, Pfizerpenn®, Crysticillin®, Duracillin®	*procaine penicillin*
Epinephrine	*epinephrine*
Isoprel®	*isoproterenol*
Benadryl®	*diphenhydramine*
Solu-medrol®	*methylprednisolone*
Colistin®	*colistimethate*
Streptomycin	*streptomycin*

Addendum

A syndrome of infant botulism has recently been described. Following an unremarkable gestation and birth, the infant develops normally until

age 5 to 13 weeks. The infant then becomes constipated and weak, as manifested by less vigorous sucking from breast or bottle, weakened crying, and loss of neck and limb muscle strength. In a word, the baby appears "floppy." Prominent physical findings include ptosis, ophthalmoplegia, reduced facial expression, dysphagia, pooled oral secretions, deminished gag reflex and poor anal sphincter tone. Generalized muscle weakness is apparent; deep tendon reflexes may be deminished or absent. Fever is noted only when associated with a secondary infection, usually pneumonia. Respiratory arrest may develop. Botulinum toxin or organisms, or both, are present in the stool. The source of this infection has not yet been delineated.[104]

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Medical Staff Conference

Whipple's Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. MORRELLI:* *This year has been marked by excellence in teaching and in management of the difficult responsibilities that fall to the chief residents. One of our chiefs, Dr. Frank Yang, will present for us now a discussion of Whipple's disease.*

Case Summary

DR. YANG:† A 63-year-old white woman of Italian origin was referred to the General Clinical Research Center at the University of California San Francisco Medical Center in May 1975 for evaluation of hypocalcemia. Her illness began in 1967 when intermittent polyarthralgias developed. Five years later she noted onset of diarrhea (characterized by chalky, bulky stools) and progressive weight loss. In March 1974 shortly after arrival in California she was admitted to hospital with severe diarrhea complicated by pneumonia. It was incidentally noted that she was severely hypocalcemic. The pneumonia responded dramatically to therapy with penicillin and she subsequently gained 30 pounds in weight.

In August 1974 the serum calcium level was normal. In March 1975 (one year following the penicillin treatment), however, she noted a recurrence of diarrhea, and in addition abdominal bloating and weight loss. In April 1975 she once again was found to be severely hypocalcemic. Treatment with vitamin D and calcium was only partially effective. She denied any fever along with her illness, her past medical history was significant only for Parkinson's disease treated for many years with trihexyphenidyl hydrochloride (Artane®) and L-dopa.

On physical examination the patient was cachectic and had mask facies. Blood pressure was 100/60 mm of mercury, pulse 90 beats per minute and the patient was afebrile. The skin was hyperpigmented and a mild glossitis was noted. There was no lymphadenopathy. Findings on chest and cardiovascular examinations were normal. The abdomen was distended, and doughy, but was otherwise normal. The stool guaiac was 3+ positive for occult blood. Trace pedal edema was noted bilaterally. The joints were found to be normal. On neurological examination a resting tremor and slight cogwheel rigidity were the only abnormalities noted.

On admission, the hemoglobin value was 11.3 grams per dl and the hematocrit reading was 33 percent with microcytic and hypochromic indices (mean corpuscular volume [MCV] 77, mean corpuscular hemoglobin [MCH] 26.1, mean corpus-

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ABBREVIATION USED IN TEXT

PAS = periodic acid-Schiff

cular hemoglobin concentration [MCHC] 33.8). The leukocyte count was 6,800 with a normal differential; prothrombin time was 12.6 seconds (control 11.9 seconds). Laboratory studies gave the following values: sodium, 134 mEq per liter; potassium, 3.5 mEq per liter; chloride 96 mEq per liter; bicarbonate, 27 mEq per liter; glucose, 91 mg per dl; serum calcium, 6.6 mg per dl; phosphorus 3.8 mg per dl; alkaline phosphatase, 132 IU per liter; serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH) and bilirubin all within normal limits; serum albumin, 2.9 grams per dl; cholesterol, 124 mg per dl; carotene, 14 μg per dl; serum iron, 32; total iron-binding capacity (TIBC), 310; B_{12}, 700 picograms per ml and folate was 20 nanograms per ml. Results on antinuclear antibody (ANA) and lupus erythematosus (LE) tests and on a Venereal Disease Research Laboratories study (VDRL) were all negative. Other values were: serum cortisol, 21.7 μg per dl; T_3 uptake, 31 percent; T_4, 9 μg per dl; IgG, 850 mg per dl; IgM, 70 mg per dl, and IgA 132 mg per dl. Stool smear showed occasional polymorphonuclear cells. Stool specimens for culture and for examination for ova and parasites were negative for pathogens. Findings on analysis of urine were unremarkable.

An x-ray film of the chest showed osteopenia but no active cardiopulmonary disease. A kidney, ureter, bladder x-ray study showed a dilated loop of small bowel with air-fluid levels on upright examination. Radiographic examination of the small bowel showed thickened mucosa generally. Electrocardiographic findings included a left anterior heart block, diffusely low T waves and prolonged Q-T interval. There was no urinary excretion of D-xylose after oral ingestion of 5 grams. A 72-hour stool fat collection—with the patient receiving a diet yielding 100 grams of fat per day—showed total fat excretion of 240 grams.

Results of a small bowel biopsy study showed typical changes of Whipple's disease with foamy macrophages in the lamina propria; periodic acid-Schiff (PAS) stain was strongly positive. Treatment was begun with penicillin, 1.2 million units given intramuscularly, and streptomycin, 1 gram administered intramuscularly each day for ten days. This was followed by tetracycline, 250 mg given orally four times a day for a year. There was prompt response to treatment with resolution of gastrointestinal symptoms and steady weight gain. When last seen, the patient was asymptomatic, had gained 30 pounds and the laboratory measures of malabsorption had returned to normal.

TABLE 1.—*Incidence of Major Symptoms in Whipple's Disease*

Major Symptoms	*Incidence (Percent)*
Arthralgia	70 to 90
Abdominal pain	70
Diarrhea	80
Weight loss	95

Discussion

Our patient today presents as a typical case of Whipple's disease. Perhaps the only unusual feature is that the patient is female. Whipple's disease was named after Dr. George White Whipple, who was an instructor in pathology at Johns Hopkins. There he encountered a 36-year-old physician with gradual loss of weight and strength. Specimens of the patient's stool were found to consist chiefly of neutral fat and fatty acids. Indefinite abdominal pain and a peculiar multiple arthritis were present. He reported this case in 1907,[1] emphasizing the anatomical finding of deposition of fat and fatty acids in the intestinal and mesenteric tissues. The disease was called intestinal lipodystrophy and was thought for a while to be a storage disease. Whipple also described a foamy cell found in the intestinal mucosa and the mesenteric lymph nodes. This foamy cell, which is now recognized as the hallmark of the disease, has been studied at length since then, especially by the use of electron microscopy in the early 1960's. The results have led to a new understanding of the cause and pathogenesis of this disease.

Several excellent reviews have been published in the recent literature on Whipple's disease.[2-4] It is a rare disorder: Miskasche and co-workers reviewed the world's literature in 1974 and found less than 250 reported cases. Patients with Whipple's disease are predominately male (90 percent of the reported cases). The disease affects mostly Caucasians and all of the cases seem to be reported in the United States and continental Europe. Only one American Indian and three black patients are reported in the literature. The peak incidence is in the fifth and sixth dec-

TABLE 2.—*Incidence of Major Physical Findings in Whipple's Disease**

Physical Finding	*Number of Patients*	*Percent*
Hypotension	140	58
Peripheral lymph nodes	111	46
Skin pigmentation	103	43
Fever	85	35
Peripheral edema	73	30
Abdominal tenderness	124	52
Abdominal distention	102	43
Abdominal mass	51	21
Ascites	26	11
Glossitis	37	15
Splenomegaly	14	6

*From Mikasche LW, Blümcke S, Fritsche D, et al.[4]

TABLE 3.—*Incidence of Abnormal Laboratory Findings in Whipple's Disease*

Abnormal Laboratory Findings	*Incidence (Percent)*
Anemia (hypochromic)	83
Hypoalbuminemia	85
Hypokalemia	45
Hypocalcemia	63
Hypocholesterolemia	60
Steatorrhea	93
Decreased D-xylose absorption	78

ades. The disease, however, has been reported in a 3-month-old baby who presented as "failure to thrive."[5]

Table 1 illustrates the major symptoms of this disease. In the early stages, arthralgia is the most prominent symptom and occurs in 70 to 90 percent of all patients. This may precede the diagnosis by from 1 to 35 years. Usually the pain is mild and migratory. Inflammatory changes of the joints are occasionally described, but joint deformity is rare. Ankles, knees, shoulders and wrists are most frequently involved, but any joint may be affected. Spondylitis has been reported, but is usually asymptomatic and is noted incidently on x-ray studies as mild arthritic changes in the sacroiliac joints. Other important early symptoms include fatigue, anorexia and fever. Fever occurs in about 40 percent of patients and can present as a fever of unknown origin. The fever generally is low grade, but occasionally can be spiking.

The diagnosis of Whipple's disease is rarely made during the early stages. By the time patients seek medical care and a diagnosis is made, the disease has entered the late stage when intestinal symptoms predominate. Nonspecific abdominal pain, usually epigastric, and postprandial bloating are noted in about 70 percent of the patients. This is followed by diarrhea (either watery or steatorrheic), as in our patient today. Gross gastrointestinal bleeding is unusual, but occult blood loss is frequent. At this stage weight loss is invariable, averaging 20 to 30 pounds, but a weight loss as great as 100 pounds has been observed. The arthralgia may improve or even disappear during this intestinal phase for reasons that are unclear. If no treatment is offered, the patient eventually dies from malnutrition and cachexia.

Table 2 is a summary of the physical findings based on 238 patients reported in the literature.[4] Mild hypotension is a relatively frequent finding. This, along with increased skin pigmentation and fever, has frequently led to the mistaken diagnosis of adrenal insufficiency. Although the adrenal glands can be involved histologically, adrenal functions are normal in those cases studied. In our patient the serum cortisol value was within normal limits.

In about half of the patients moderate peripheral lymphadenopathy is present. Abdominal examination generally shows diffuse tenderness and distention. Occasionally enlarged mesenteric lymph nodes may present as palpable masses. Ascites is unusual and may be chylous in nature. Finally, splenomegaly is a rare finding in this disease.

Table 3 summarizes the laboratory findings, which generally reflect malabsorption. Nonspecific anemia is seen frequently. Since in these patients malabsorption of vitamin B_{12} or folate usually is not present, megaloblastic changes are uncommon. In our patient both serum B_{12} and folate levels were normal.

Hypoalbuminemia is frequently seen and probably is due, in part, to gastrointestinal protein loss. Laster and associates[6] injected radioactive albumin into patients with Whipple's disease and were able to recover significantly greater amounts in stool specimens than were found in those of normal controls. This abnormality corrects rapidly with treatment. In addition, a lower albumin turnover rate occurs in these patients indicating impairment in the synthesis of albumin.

The hypocalcemia and elevated alkaline phosphatase are consistent with osteomalacia secondary to steatorrhea and malabsorption. Steatorrhea is almost uniformly present in the late stages of the disease and sometimes can be extreme. D-xylose absorption is also abnormal in about 80 percent of the patients.

The definitive diagnosis of Whipple's disease is

made by showing the presence of PAS-positive macrophages in the mucosa of small bowel which can be easily obtained by per-oral small intestinal biopsy.

Figures 1 and 2 illustrate the typical histological changes seen on a biopsy study of the small bowel. The villi are blunted in severe cases, but the hallmark of the disease is infiltration of the lamina propria with foamy macrophages which stain positively with PAS stain. These macrophages may also be found in the mesenteric lymph nodes and, in fact, in many other tissues in the body.

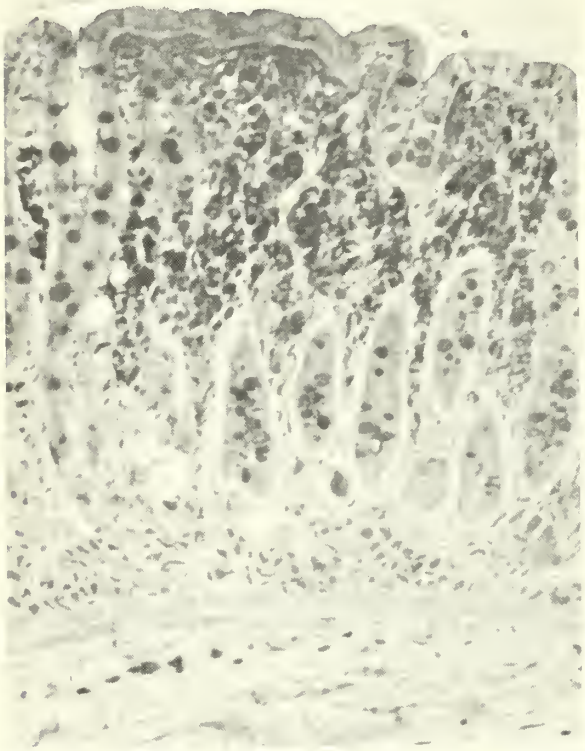

Figure 1.—Small bowel biopsy specimen stained with periodic acid-Schiff stain showing many PAS-positive macrophages.

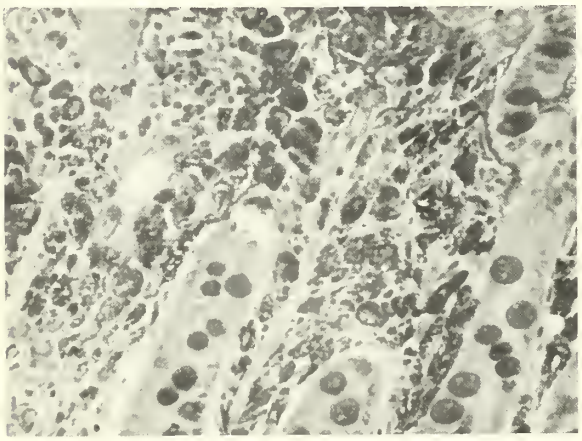

Figure 2.—Close-up of macrophages laden with PAS-positive material.

The colon and rectum can be involved but one must be careful in interpreting the presence of PAS-positive macrophages in the rectal mucosa since this can be a normal finding. The fact that Whipple's disease is a systemic disease is usually not emphasized. Peripheral lymph nodes are frequently involved and sometimes serve to confirm the diagnosis. Occasionally the histology of lymph nodes can suggest sarcoid or lymphoma. Cardiac involvement is frequently found at autopsy. For example, pericarditis is present in about 80 percent and endocarditis involving the mitral and aortic valves in about 25 percent of the cases. However, clinical symptoms attributable to these lesions are rare.

Neurological involvement may produce a wide spectrum of symptomatology—from changes in mental status to spastic paresis. Cerebrospinal fluid findings usually are normal. Although arthralgia is a prominent symptom, very little is known about the pathological changes within the joint. Only nonspecific synovitis has been found in histological studies of biopsy or autopsy specimens.

The nature of the foamy macrophages and their role in this disease have been extensively studied since Whipple's original description. In 1949 Black-Schaffer[8] first discussed the role of PAS-positive staining, characteristic of these macrophages. Later, Sieracki[9] found the macrophages to contain sickle-shaped granules. He called it the SPC cell, standing for the sickle form particle containing cells. These granules stained positively with the PAS stain. Whipple's original case was subsequently studied and also showed the typical changes of PAS-positive macrophages.

In the early 1960's two independent groups of investigators[10,11] studied tissues from patients with Whipple's disease using electron microscopy. They both reported rod-shaped bacillary bodies in the lamina propria of the small intestinal mucosa and within the macrophages. Now confirmed by many investigators, this appears to be a universal finding in active cases. By careful sectioning and staining one can see the bacilli by light microscopy as well. In fact, in his original report Dr. Whipple himself had called attention to a rod-shaped organism found in one of the lymph nodes.

A typical bacillus viewed by electron micros-

copy measures approximately 1 micron in length and 0.2 micron in diameter and has a cell wall closely applied to a typical triple-layered cell membrane. It is found to be most abundant in the extracellular spaces in the lamina propria before treatment is begun. These "bacillary" bodies have now been shown to be present in the intestinal mucosa, the mesenteric and peripheral lymph nodes, the brain and also the heart of patients with Whipple's disease. Electron microscopic studies have shown phagocytosis of these bacilli by macrophases leading to the formation of intracellular granules. The bacilli then undergo distintegration and ultimately form particles of closely packed membranous material. The particles containing these membranes are equivalent to the sickle-form particles described by Sieracki[9] and stain positively with PAS stain. They may remain for years after successful treatment, whereas the extracellular bacilli disappear within a few days after treatment has begun.

Although the bacilli are found most abundantly in the intracellular spaces and within the cytoplasm of macrophages located in the lamina propria, they have also been shown to involve the absorptive epithelial cells, and likely contribute to their diminished function. Brice and co-workers[12] have found decreased amino acid uptake and decreased capacity to reesterify free fatty acid by the intestinal mucosa from patients with Whipple's disease. Morphological changes in the intracellular organelle also suggest abnormal lipid metabolism. After a fatty meal there is normally an accumulation of lipid in the smooth endoplastic reticulum where reesterification of free fatty acid occurs. This intracellular process is decreased in patients with Whipple's disease.[3] These data suggest that this is an important contributing mechanism to fat malabsorption. This is further supported by the close correlation between functional and structural improvement following antibiotic treatment. Additional possible mechanisms of malabsorption include: a reduction in epithelial cell mass; physical impedance of chylomicron transport to the central lacteals by the presence of a great number of macrophages within the lamina propria; obstruction of lymphatic flow secondary to enlarged mesenteric nodes, and, finally, functional damage to the lymphatic endothelium.

Before the use of antibiotics, Whipple's disease was invariably fatal. In the early 1950's treatment with corticosteroids was common. Patients treated with steroids alone usually showed early clinical response, but quickly relapsed. Scattered reports of dramatic response to antibiotics then began to appear in the literature, but it was not until 1963 that Davis and associates[13] showed antibiotics to be invariably effective and that prolonged treatment was necessary to prevent relapses. They recommended therapy with penicillin, 1.2 million units, and streptomycin, 1 gram a day for ten days, followed by tetracycline, 1 gram per day for 10 to 12 months. With this regimen, no recurrence of symptomatology was observed in 12 patients.

The clinical response to therapy is dramatic and within a week patients begin to feel better and diarrhea subsides. Significant weight gain quickly follows and within six months all laboratory abnormalities will have reverted to normal. As previously mentioned, the PAS-positive macrophages may persist for many years and, therefore, are not a useful measure of improvement. The most sensitive histological change is the disappearance of extracellular bacillary bodies which generally occurs in a few days. The reappearance of these bacillary bodies heralds a relapse.[14]

Based on morphological data, and the fact that patients invariably respond to antibiotics, most investigators agree that Whipple's disease is an infectious disease. However, as yet no one has convincingly isolated the bacteria nor reproduced the disease in an animal model. Many bacteria have been isolated, but contamination has always been a possibility.

Recently isolation of an atypical bacterium from jejunal mucosa and peripheral lymph node has been accomplished.[15] On subsequent subcultures reversion back to an alpha hemolytic Streptococcus occurred. This organism appears to be a facultative intracellular parasite and its incubation with human fibroblasts causes accumulation of PAS-positive material within the cultured cells. Demonstration of serum antibodies against the bacteria has been accomplished by indirect immunofluorescence. Finally, when the organism was injected into a rabbit, a systemic disease characterized pathologically by the accumulation of PAS-positive material within macrophages developed.

Atypical bacteria have been isolated previously by other investigators. Charache and co-workers[16] isolated a bacterium from six different blood cultures and from a peripheral lymph node in a patient with Whipple's disease. The organism ini-

tially required hypertonic media for growth and took a pleomorphic form. On subsequent subcultures, however, the organism reverted back to a beta hemolytic Streptococcus and when ingested by leukocytes *in vitro,* it formed particles the same size as the bacillary bodies seen in Whipple's disease. The organism isolated by these authors was not pathogenic in mice and rabbits. These reports do not constitute conclusive proof of a cause-and-effect relationship and much more work is needed to clarify this matter.

Much has been learned about Whipple's disease since its original description, but there remain many unanswered questions. Why is it a rare disease? What is the explanation for the age and racial preferences and its striking geographic distribution? What host factors predispose to development of Whipple's disease? Several recent reports have focused on the possibility of immunologic defects. Unfortunately, most of these studies are carried out using isolated cases and it is difficult to draw meaningful conclusions from them. Although in occasional patients immunoglobulin deficiency has been shown, impaired humoral immunity is not a consistent finding. Our patient had normal immunoglobulin levels.

Aberrations in delayed cutaneous hypersensitivity have been found in patients with Whipple's disease.[14] These are associated with an *in vivo* alteration of lymphocyte function. In nine patients with treated Whipple's disease (studied at ten months to 16 years after antibiotic therapy) delayed hypersensitivity reactions were significantly depressed. Phytohemagglutinin-induced tritiated thymidine incorporation by peripheral lymphocytes cultured in autologous plasma was consistently decreased in eight patients in comparison with similar studies of 11 control subjects.[14] Further investigations are necessary to elucidate the role of impaired cellular immunity in the pathogenesis of Whipple's disease.

A new case of Whipple's disease has been presented here and the clinical and histological features of the disease discussed. Although several observations suggest an infectious cause, the organism remains obscure. Impaired cellular immunity may be a predisposing factor but its exact role in the pathogenesis of the disease remains unclear. It should be emphasized that the diagnosis of Whipple's disease can be confirmed rather easily by a per-oral biopsy study of the small intestine, yet early diagnosis is seldom made. Once the diagnosis has been established, antibiotic treatment is invariably curative.

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Important Advances in Clinical Medicine

Epitomes of Progress—Industrial Medicine and Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Industrial Medicine and Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Industrial Medicine and Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Industrial Medicine and Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Fiberglass—Not Carcinogenic

FIBROUS GLASS has been used in the economy for decades—in homes, in transportation and in industry. Because of the established relationship between asbestos and disabling lung disease, mesothelioma and carcinoma of the lung, substitutes have been sought for typical asbestos applications. Fiberglass has replaced the naturally occurring material in shipboard use, serving as an insulating material on heat-generating and heat-carrying systems. In some instances, such as in gaskets used with extremely high-pressure, high-temperature vessels it has not been possible to use fiberglass as a substitute for asbestos because it cannot withstand the temperatures encountered.

Some investigative opinion has hypothesized that because it is fibrous, glass in this form may be an inhaled human carcinogen. Contemporary analysis of work done substantiates the classification of this material as inert. Evidence of fibrous glass causing human occupational cancer is minimal, and is heavily outweighed by the evidence against it. Current opinion is that fiberglass is a substance with no long-term occupational toxicity or public health hazard in humans, in spite of fears expressed by some.

Glass as a fiber remains solely a short-term mechanical irritant of the skin, and as a rare invader of the skin or pharynx, it causes a typical foreign-body reaction.

In spite of labor-management agreements allowing higher pay to those in industry who work with fiberglass, no solid evidence points to its role as a carcinogen or inciter of chronic pulmonary disease.

J. S. FELTON, MD

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Ethylene Oxide Burns

STERILIZATION of surgical dressings, gowns, anesthesia and inhalation equipment, and other medical supplies using ethylene oxide gas has become the favored method in many hospitals in recent years. Ethylene oxide is a colorless, gaseous, simple epoxy compound capable of producing severe burns in patients and hospital personnel. The scald-like lesions resemble bullous impetigo and toxic epidermal necrolysis (Lyell's disease).

After sterilization by this method, articles must be aerated thoroughly to insure that all residues of gas are eliminated. Polyvinyl or rubber materials should not be used within seven days following sterilization if stored at room temperature.

ROBERT M. ADAMS, MD

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Preemployment Radiography of the Spine

FOR YEARS both physicians serving industry and orthopedists providing consultative service to employers have debated the worth of preemployment radiography of the spine. Of particular concern has been the so-called "congenital anomaly" as the causative bête noire of back injury.

The literature on this subject falls into three broad categories. One includes articles that report only the incidence of abnormal x-ray findings noted on standard examinations with no relationship to clinical back symptoms or injury. Such information does nothing to establish a basis for the use of preemployment spine x-ray studies. A second includes reports that proclaim a reduction in the incidence and severity of back injuries following the institution of preemployment radiography of the spine to exclude persons with defects presumed to be significant. While such writings cannot be ignored, they do use a different comparative time period—many not fully taking into account increased safety efforts and the effect of greater attention given back complaints as a result of their programs. A third category is made up of articles in which the spine x-ray studies of persons with back symptoms are compared with studies of persons without back complaints. If spine x-ray studies do have predictive value, one would expect an increased incidence of abnormalities discoverable on x-ray films among those persons with complaint of back difficulty. Analysis of such studies showed that most investigators failed to find significant differences in the number of abnormal lesions. The conclusion of the author, after reviewing 56 publications, was that the use of preemployment x-ray studies of the back has been based primarily on the hypothesis that developmental abnormalities predispose to an increased incidence of lumbar back injury. Evidence would show that this hypothesis has not been substantiated.

No mention has been made of the findings by interested radiologists that many of the heretofore termed congenital anomalies were, in fact, posttraumatic in nature, being found after stress fractures. Further, no discussion was devoted to the matter of the intensity or depth of ionizing radiation required for a variety of views of the lumbosacral spine, including usually anterior-posterior, lateral and two oblique exposures. The upsurge of malpractice accusations, in addition to the arguments offered above, should end the use of preemployment spine radiography as part of a pre-hiring examination by either in-plant physicians or private practitioners who examine for industry.

J. S. FELTON, MD

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Alcoholism and Workers

PRACTITIONERS who help industry comply with federal and state laws and regulations in occupational safety and health may be faced with an employer who cannot resolve the job performance problems of several capable, but frequently absent, employees who are chronic alcoholics. The consultant may recommend to the company that an alcoholism rehabilitation program be established consisting of three parts: (1) the publication of a policy regarding the employer's recognition of alcoholism as an illness and his support of a program devoted to conserving work-contributing problem drinkers; (2) the ori-

entation of the first-line supervisor so that he can effect his role in recognition, confrontation and referral and (3) the presence of a medical and counseling capability within the organization to bring about extramural referral and treatment along with supportive counseling during the period of newly attained sobriety.

Labor, management, the federal government, the Armed Services and other major groups have established policies and have created mechanisms for the identification and treatment of alcoholic employees so that the 9,000,000 alcoholics in the United States can be retained in, or returned to, gainful employment. Concerned practitioners working in occupational medicine or acting as consultants to commercial or manufacturing organizations can aid an employer in rehabilitating potentially productive workers whose illness now costs American industry more than $12 billion a year.

J. S. FELTON, MD

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Effect of Noise: Psychosomatic Reactions to Acoustic Shocks

NOISE is defined as any unwanted sound. Prolonged exposure to noise eventually can produce measurable hearing loss. Noise also may produce physiologic changes: dilation of the pupils, increased pulse amplitude and rate, impairment of sleep, annoyance reactions, startle reactions and manifestations such as nausea, headache, irritability, instability, anxiety and loss of appetite.

Very loud noise of short duration is called impulsive noise and is exemplified by the sound of gunfire. This type of noise is more likely to result in a severe startle reaction, especially if not anticipated, and may result in more than the usually measurable physiologic body responses.

A case in point involves a middle-aged telephone operator who was startled by a loud noise when she plugged into a telephone line. There was an immediate outcry, and a prompt loss of consciousness. Upon arousal she had pain and tinnitus in the ear, nausea, vomiting, diaphoresis and severe anxiety. This person never returned to her job. She developed a profound fear of telephone equipment (conversion hysteria?) and required continuing (lifelong) psychiatric care.

Acoustic shocks in the telephone industry may occur in flurries. One operator at a bank of switchboards may be a victim of impulsive noise on the line and the person's outburst often results in similar responses in co-workers soon after. In some instances these employees must be transferred to other work because they become extremely apprehensive and report acoustic shocks frequently and in rapid succession, although the equipment is found to be in excellent working order.

Noise is of considerable concern to the Occupational Safety and Health Administration and its counterparts on the state level, as it is to the United States Environmental Protection Agency and the community at large.

ANTHONY A. MIRA, MD

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Degreaser's Flush

TRICHLORETHYLENE (TCE) is one of the most widely-used industrial solvents, serving as an effective degreasing agent for metal parts in addition to other uses. Recent observations of persons repeatedly exposed to TCE vapor showed the sudden occurrence of a blotchy, red eruption a few minutes following the ingestion of moderate amounts of enthanol. The vasodilatation of small blood vessels involves bilateral and fairly symmetrical areas of the face, neck, chest and back, and occasionally also the extremities. The erythema, while embarrassing to the worker, is not accompanied by unusual subjective responses. Blood pressure, pulse and findings on electrocardiogram, complete blood count, urinalysis and SMA-12 panel are within normal limits. The condition usually subsides in a few hours.

This response to TCE vapor has not been recognized before, and has eluded satisfactory explanation. While apparently quite harmless, degreaser's flush requires further study.

ROBERT M. ADAMS, MD

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Health Assessment by Nurses in Industry

To comply with public demands for more health practitioners, the role of nurses has been expanded to allow them to assume some of the functions previously considered unique possessions of a physician. For roughly a decade some nurses in industry have received special training so that they first were able to take preemployment histories, and in later years they could conduct preemployment medical examinations.

In almost all cases these programs have been highly successful because the university-based training programs provided intensive course work that was given clinical substance by physician-based preceptorships. In the health facility of one manufacturing plant a study was conducted of 402 consecutive health assessments done by registered nurses and a qualified technician. These examiners did 85.1 percent of all health assessments—sharply reducing the physician's workload—and performed well. Almost no significant clinical disorders were missed. Those problems that did arise after employment were such that the preemployment examination would not have detected the deficit. Applicants with severe physical disabilities were appropriately referred to the physician.

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Psychiatric Patients and Work

With federal and state legislation requiring greater employment of the handicapped, applicants with physical and emotional limitations are entering the labor force more than ever before. For decades, employers have been apprehensive about personnel with psychiatric problems.

At the large American headquarters of one international business-machine manufacturing corporation, a consulting psychiatrist was available to the medical department three hours per day. Studying 135 employees (some of them self-referred, some referred by others), two- to three-year follow-up showed that 61.7 percent were still with the company. Of these, 10 were rated outstanding, 38 exceeded job requirements, 25 were meeting job requirements and 4 were not meeting job requirements.

Of 83 employees rated unsatisfactory at the initial referral, 49 were doing satisfactory work at follow-up. The study emphasizes the worth of a full-time medical department that offers psychiatric consultation facilities leading to secondary and tertiary prevention.

In a related review based on a questionnaire study of 161 supervisors in both government and nongovernment employment, it was confirmed that employees seeking help from a psychiatrist are likely to experience varying degrees of negative attitudes from supervisors at work. The advice given to employees in therapy was "Don't tell your boss." The observers' feeling was that dishonesty may be the best policy.

With all illness coming into the open, it is believed that frankness still is the only avenue to total acceptance of an involved person. Employers will learn, in time, that nearly every persson, given the opportunity for work *and* care, will prove effective.

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Biological Dysrythmia in Transmeridian Jet Travel

Recent investigation into the changes in physiologic function in humans as a result of jet travel across international time zones has confirmed the findings that the normal cyclic variations in activity in a 24-hour period, such as body temperature and adrenocortical secretions, are indeed disrupted by travel west to east and vice versa. These reflexes are cued by day-night stimuli and adjust the organism so that optimum function is present when needed; unfortunately, the cuing takes days to readjust to a new environment. Of great importance to a traveler is the ability to think clearly, which in his accustomed environment reaches a low point at 4:00 a.m. It becomes clear, then, that a time differential such as that experienced between San Francisco and London could find the business traveler at a relative disadvantage for making important decisions. Fatigue, coupled with paradoxical in-

somnia, anorexia, headache and dehydration further contribute to the discomfort of people traveling for either business or pleasure.

There is minor discomfort associated with travel beyond two or more time zones. Beyond five zones, a full day should be provided for convalescence after travel. Management of this syndrome is supportive because the problems are self-limiting. Some of the above symptoms can be modified by resting before long air journeys, by carefully planning itineraries and by avoiding last-minute packing and bon voyage parties. The natural tendency to overindulge in good food and drink before and during a trip should be avoided. Finally, the physician prescribing for the traveler should consider the altered biologic clocks of his patient, particularly a patient with diabetes mellitus.

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EDITORIALS

A BICENTENNIAL EDITORIAL

Another "War" for Independence?

THE FOUNDING FATHERS of this nation were concerned with independence and with establishing a government that would serve the people and rid them of tyranny. They could not foresee the extent of the technological, social, economic and political interdependence that was to become a reality by the time of this bicentennial year. Nor did they foresee the huge and unwieldy bureaucracy that would come into being in the effort to deal with it. The full extent and meaning of the interdependence is yet to be fully comprehended in not only its national but its worldwide ramifications. But it is becoming clear that a major problem for America in its third century will be how to maintain some degree of freedom and independence within a framework of increasing interdependence. Boiled down, the issue is whether the people of this nation can any longer govern themselves or must they be governed and told what they may and may not do by an often impersonal and remote government, much as was the case in 1776.

This issue and its attendant problems are certain to plague third century America. They are already coming into focus in the field of health, where the question of governance for the health care enterprise in this nation has become a critical one. The health industry, one of the largest in the nation, is the first such that the federal government is trying to regulate and control in its entirety, and this is because the ramifications of the growing interdependence first became acute in this field. It all stems from technologic success. The quality of American medicine is the highest in the world. The fact is that American medicine can now do more for more people than we are willing to pay for. And besides being a scientific and technologic enterprise, medicine and health is a deeply human affair which is especially important when health is not there or is lost. It is very clear that America now wants more health, more health care, more well-being and more quality of life—and wants more of it per dollar. So, it is in medicine and health care that the realities of technologic achievement, rising aspirations, expectations and costs; and growing social, economic and political interdependence have now reached critical proportions. And it is in medicine and health care that the precedents for solving these emerging problems of American and eventually of world society may be set.

Governments are formed for the purpose of governing and our American government is no exception. Particularly, and uniquely for the times, it was formed to serve rather than to rule the people, and to govern with the consent of the governed. But over the years a governmental giant came into being—a giant which has become so large and powerful that it is sluggish in motion, inefficient in performance and unbelievably costly to feed and maintain. It is this giant to whom the responsibility has fallen to try to regulate and control the health enterprise of this nation. It so happens that the giant knows only one way to do things. This is to pass laws, make regulations which have the force of law, extract dollars from taxpayers, and allocate or withhold dollars as suits its purpose. It is these powers that made the giant a giant and since it knows no other way, it may be expected to resist any effort to forestall, change or reduce its powers. Knowing no other way, it is now using these familiar tools to regulate every aspect of the health care industry—manpower education and training, research, services to people and even drugs, equipment and supplies. The result is that the government giant is beginning really to control and rule the lives of people, or at least a segment of the people—those who are the providers and recipients of health care services—while of course at the same time observing the conventional rhetoric, which holds that government has the duty to impose whatever rules, regulations, incentives and deterrents it deems necessary in the service of the taxpayers and the public. The possibility of tyranny is clearly present if this approach suc-

ceeds in health and is extended to other fields, and the future of independence within what must from here on be a framework of increasing interdependence is uncertain at best.

It is the reality of technological, social, economic and political interdependence—with all its implications—that must be faced. This will not go away, nor can it safely be ignored. Rather it will bring greater problems, and new techniques for governance will be needed to solve them. If the trend to rule by government bureaucrats is to be reversed, some means of returning at least some of the decision making to the people who are involved must be found. The health enterprise is now at the interface where this may or may not be done depending upon what ingenuity and leadership is shown. What is done or not done is likely to set the precedents for what happens in other fields and indeed for the next century of America. It is therefore a serious matter.

At first sight it might seem that the government giant has the overwhelming advantage with its accepted and deeply entrenched powers, and because it has assumed the battle initiative by invading the field of health care on a very broad front. But it is suggested that this advantage may not necessarily be as real as it seems. For one thing the government giant is weak in spite of its great size. The fact is that it is not doing a good job and probably it cannot. Perhaps its greatest strength may even be its greatest weakness. It may be that simply passing more laws, making more regulations, creating more agencies and allocating or withholding more dollars only compounds the problems and are actually counterproductive. It already seems so. But this is the only approach the giant knows and although it is ill suited to solving the problems of the health enterprise it will be continued. Sooner or later the public will become disenchanted, fed up with rising costs, increasing government restrictions and poor results. The first question, important as it is, "Who will get the blame?," is not as important as the second question, "Will there be an alternative method available for the governance of health care when the time comes?"

The issue really gets down to whether government is to be master or servant of the people in their day-to-day lives, and to what extent can the people be involved in the decision making which affects them and what they do, and to what extent can they have the power of consent. In short, how can the people exercise some personal and professional independence within the now inescapable framework of national and even worldwide interdependence.

What may be needed is for another "war" for independence to be waged at this time by America's health enterprise. It should be led and coordinated by medicine. It should be a preventative war in behalf of the public against impending tyranny by government. Its stated purposes should be acceptable to all segments of the health enterprise and to the public. The strategy should be at least three pronged: (1) expose and exploit the weaknesses and mistakes of the federal bureaucracy whether in the administrative or legislative branches of government, (2) identify and define the needs and concerns of the public and groups within the public and become their advocate and (3) perhaps most important, develop an alternative to federal rule of the health enterprise which will allow for some internal governance (with some independence and provision of some consent of the governed) within the framework of technological, social, economic and political interdependence that now exists and will continue henceforth.

The Goliath of government may not be all that invincible, particularly if David takes good and careful aim with his slingshot.

—MSMW

The Biological Substrates of Mental Illness

It is an interesting paradox that the antipsychiatry movement and its opposition to the medical model of mental illness has achieved prominence and some influence at a time when that model and the sciences on which it depends have made gratifying progress in the treatment of the major mental illnesses and have elucidated some of the neurobiological processes on which an understanding of their causes and pathogenesis may well depend. In the past 25 years new drugs have become available and widely applied with salutary specificity against the cardinal, incapacitating symptoms of mental disorder[1] and fundamental knowledge in the rapidly growing neurosciences has supplied the basis for explaining their mechanisms of action.

The first of the phenothiazines was introduced

into psychiatric treatment in 1952.[2] These agents, as well as the butyrophenones and more recently developed antipsychotic agents, have been found to ameliorate the disturbed thought and behavior of schizophrenia in many patients. Iproniazid was abandoned in the treatment of tuberculosis because of its tendency to produce excitement in some patients. What was a deleterious side effect in that application, however, was found to be a therapeutic benefit in the treatment of depression. This and other monoamine oxidase inhibitors were followed by the tricyclic antidepressants. The first and most dramatic effects of lithium were seen in the treatment of mania, which was then followed by the demonstration of its effectiveness in preventing recurrences of depressive as well as manic episodes. All of these drugs are different from the agents previously available to psychiatry in the specificity of their therapeutic effects. Although the barbiturates were able to control disturbed behavior they did so only in dosages that would notably depress a normal person. On the other hand, the usual antipsychotic dosage of chlorpromazine, the tissue concentrations of lithium which will relieve mania, or the dose of imipramine effective in treating depression, produce little, if any, effects on normal thought or mood. Through psychopharmacology the controlled clinical trial was introduced into psychiatry, by means of which the effectiveness of these drugs was shown, some time before their mechanism of action was understood. But although these drugs undoubtedly act on biological processes, it could still be argued that they afford symptomatic treatment of dysfunctions that are not necessarily biological in origin.

In the past ten years research has been conducted on adopted persons and their families to disentangle their genetic endowments from environmental influences. In each of several studies the biological offspring,[3] or the siblings and parents[4] of schizophrenics, with whom they have not lived, have a significantly increased prevalence of the disorder, while the adoptive parents who reared them and the adoptive siblings who shared their environments show no more schizophrenia than do members of the general population. This represents rather compelling evidence for the operation of genetic factors in schizophrenia. If that is the case, then biochemical processes must also play a crucial role, since the genes can express themselves only through biochemical mechanisms.

Fundamental research in the neurosciences and the knowledge it provided over this time have given meaning and direction to the empirical therapeutic and genetic observations. Among the important discoveries that neurobiology has made, probably none had a more important impact than the discovery of the chemical nature of the synapse. It is now clear that the brain is not simply a complex electronic computer, but one in which chemical and electrical processes interact at every level. Through the submicroscopic synaptic cleft pass chemical neurotransmitters that are synthesized and released from one neuron to affect specific receptors in the next. There is no doubt that the higher nervous activity that is especially characteristic of man and includes perception, cognition, motivation, mood and thought must be mediated through the synapses of the brain. Their chemical nature provides crucial loci at which genetic expression, metabolic processes, hormones and drugs may affect these psychological processes. If there are biochemical disturbances in mental illness, one would expect them to operate there, and it is at the synapse where the drugs ameliorating these illnesses should exert their influence.

It is now clear that all of the antidepressant drugs have important actions on certain synapses, enhancing, by one mechanism or another, the actions of norepinephrine, serotonin and dopamine, and quite possibly affecting other transmitters less well defined.[5] Reserpine, which can occasionally produce a state practically indistinguishable from endogenous depression, depletes synapses of these transmitters. It has been shown, at chemical, physiological, molecular and clinical levels, that all of the drugs effective as antischizophrenic agents act on dopamine synapses to attenuate their activity.[6]

In his paper "Neurochemistry and Behavior in Man" which appears in this issue, Omenn succinctly and lucidly reviews the burgeoning field of neurobiology as it applies to human behavior and neuropsychiatric disorder. The monoamine transmitters have been the center of most of the research effort and much has been learned regarding their metabolism, release, inactivation and postsynaptic effects. Certain amino acids have systematic effects at particular central synapses which are under careful study; and certain polypeptides, characterized at first as pituitary releasing factors from the hypothalamus, undoubtedly have more widespread effects throughout the

brain. The psychobiology of all of these synaptic transmitters and modulators remains less clear and our knowledge is fragmentary. There is enough information to indicate quite clearly that they interact with each other in complex patterns to mediate aversive and appetitive behavior, attention, memory and mood. How they do so, and what derangements in their normal function occur in the major mental illnesses are questions that can now be plausibly addressed.

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SPECIAL EDITORIAL

Radiation Risks of Mammography

IN THIS DECADE of increased public awareness of environmental hazards, it is hardly surprising that extensive publicity be given to statements on the potential carcinogenic effects of widely-used x-ray examinations. Such adverse publicity has recently been circulated concerning mammography, publicity that unfortunately contains many inaccuracies and gross overstatements.

Mammography is a valuable diagnostic tool for detection of breast cancer. When used in conjunction with physical examination, the diagnosis of carcinoma can be made with a high degree of accuracy, especially in women over age 50.[1-3] Mammography is particularly useful in discovering early breast cancer. Fully a third of the early cancer found among asymptomatic women is found by mammography alone;[4,5] this applies equally to women above and below age 50.[6]

Despite these proved advantages, the full benefits and potential risks of mammography are not fully known. For these reasons and others the American Cancer Society (ACS) and the National Cancer Institute (NCI) jointly are sponsoring a nationwide breast cancer detection project designed to screen 270,000 asymptomatic women. It is hoped that this project will result in a determination of the proper role that mammography should play in detection of early breast cancer. Specifically, information should be forthcoming on (1) the optimal age for the initial mammogram, (2) the proper frequency of screening mammograms and (3) whether or not there are significant long-term radiation risks.

There is a wealth of information on the carcinogenic effect of *large* doses of x-rays (100 rads or more). However, despite numerous controlled animal experiments and extensive epidemiologic analyses of human cancer, remarkably little is known of the sequelae of *low* doses of radiation, especially in the range in which mammography now functions (0.5 to 5 rads surface dose, breast tissue dose substantially lower). In fact, there is no hard evidence of x-ray induction of cancer in any adult human being with radiation doses less than 50 rads;[7] specifically for the breast this limit appears to be 90 rads.[8-11]

In order to apply the data from high-dose studies to the much lower doses used in diagnostic radiology, most radiobiologists construct a dose-response curve and extrapolate linearly back toward zero, assuming that there is no threshold dose below which carcinogenic effects are absent. However, this type of approach is misleading, especially since the calculations result in highly specific conclusions having the ring of scientific accuracy. In fact, such analyses are based on assumptions that have never been proved, and about which there is considerable disagreement.[12-14] Conclusive evidence does not exist for either a linear dose-response curve or lack of a threshold dose.[12-15] Therefore, even the most impressive statistical analysis that leads to these assumptions must be considered inaccurate, with the probability that this inaccuracy will result in significant overestimations of risk.[15-16]

The recent analyses that have received national press coverage attempted to evaluate the benefits and cumulative radiation risk of multiple mammographic examinations in asymptomatic women. These analyses by Bailar[16] and Breslow[17] were based on the best available study (the HIP [Health Insurance Plan of Greater New York] study) of

screening mammography, begun in 1963, which showed a substantial reduction in breast cancer mortality only for women over age 50.[1,5] Breslow used the HIP study to conclude that screening mammography under age 50 was not recommended, but that the benefits outweighed the risks in women over 50. Neither Breslow nor Bailar attacked the advisability of single mammographic examinations, probably since the resultant radiation doses were so small. However, both analyses suffer from two serious weaknesses: (1) the risk analysis was based on the unproved assumptions of a linear dose-response curve and lack of threshold dose and (2) no allowance was made for the improvements in mammographic equipment, technique and knowledge that have accrued in the greater than ten-year interval since the HIP study mammograms were taken. These improvements are illustrated by preliminary data from the breast cancer detection project, which show that a third of the breast cancer so far detected has been in women under age 50, and that 45 percent of this cancer was detected by mammography alone.[6]

Unfortunately, the effects of the Bailar and Breslow analyses have been quite far-reaching, almost certainly due to extensive and misleading lay press coverage. By elevating what are in fact unproved estimates of risk to the status of scientific acceptance, the press has unduly alarmed the public about radiation hazards of mammography. This error is further compounded by grossly overstating the conclusions to apply to all mammography situations rather than only to multiple screening examinations in women under age 50. Headlines such as "Breast Cancer: Does One Exam Cause a Tumor?"[18] are to be deplored.

One adverse effect of this publicity has been a substantial reduction (as much as 30 to 40 percent) in mammographic examinations across the country, not only among asymptomatic women above and below age 50 but also in women with signs and symptoms suggesting the presence of breast cancer. Of the many women who are now avoiding mammography, some most probably have early cancer detectable only by the examination they have been misled to refuse. This will inevitably result in isolated individual tragedies.

More disturbing is the recent decision of the ACS and NCI to recommend against mammography for asymptomatic women aged 35 to 50 in their nationwide screening centers. This amounts to abandonment of a portion of the breast cancer detection project, a step backwards which will result in loss of the very benefit-versus-risk data that promise to indicate accurately the extent to which screening mammography is advisable. It is ironic that the ACS-NCI decision is based on the same inadequate and probably inaccurate data that helped prompt the breast cancer detection project in the first place; and it is unfortunate that the ACS and NCI seem to have based their decision on public reaction to misleading and overstated media reports rather than on any conclusive scientific evidence.

Now is the time to put the situation straight. To that end I offer the following suggestions. (1) Mammography should remain an integral part of the evaluation of women who have symptoms or physical findings suggestive of breast cancer, regardless of age. (2) Screening mammography in asymptomatic women over 50 should continue to be done at regular intervals since even now there is general agreement that its benefits outweigh the risks. (3) The ACS and NCI should reverse their decision and encourage screening mammography in asymptomatic women in the 35 to 50 age group. The data to be compiled from the nationwide breast cancer detection project currently offer the best hope for determining the proper role for mammography for women of all ages. Let us not abandon this hope because of admittedly insufficient risk evidence, especially since preliminary findings of the screening project indicate substantial benefits for women under 50. (4) Mammography should be carried out at the lowest possible radiation dose consistent with current diagnostic accuracy. Radiologists should strongly consider using high-filtration xeroradiographic techniques or the even lower dose screen-film systems that have recently been marketed. Mammography done in this fashion produces a fourth or less radiation than assumed in the calculations of Bailar, and even allowing for his inaccurate analytic methods would shift his conclusions clearly in favor of mammography.

All involved in the current mammography controversy agree that we know too little about radiation risks to draw firm conclusions. Some, relying heavily on the "best" evidence now available, would limit the scope of mammography until more conclusive data can be generated. I must remind them, however, that no animal experiments and no retrospective statistical analyses can produce data any more meaningful than those which are available now. Rather, we must design

prospective clinical studies to determine benefits and risks as accurately as possible. Such studies, of course, should require informed consent of all participants. The most promising attempt to date has been the joint ACS-NCI project.

Mammography is already known to be beneficial for symptomatic patients of all ages and for the screening of asymptomatic women over 50. Let us now find out whether this also applies to the screening of women under 50 by proceeding with the breast cancer detection project without alteration or delay.

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EDITOR'S NOTE: The above editorial was sent to Lester Breslow, MD, for comment. Dr. Breslow's views are presented below. A reply from Dr. Sickles will appear in the Correspondence section next month.

Radiation Risks of Mammography: Another View

IT IS PROBABLY TRUE that recent and unfortunately sometimes misleading publicity has created some undue alarm about the risks of mammography. Matters are not set straight, however, by statements such as that of Sickles. He touches mainly on two points.

One point advanced by Sickles can be represented by quoting from his editorial:

". . . potential risks of mammography are not fully known."

". . . most radiobiologists construct a dose-response curve and extrapolate linearly back toward zero, assuming that there is no threshold below which carcinogenic effects are absent."

". . . such analyses are based on assumptions that have never been proved, and about which there is considerable disagreement. Conclusive evidence does not exist for either a linear dose-response curve or lack of a threshold dose."

In our report to the National Cancer Institute of 15 July 1976,[1] we stated:

"The basis for believing that mammography may induce breast cancer lies in a series of studies indicating that exposure of the breast to radiation can cause breast cancer. These studies show that women (a) exposed to radiation in the Japan atomic bomb explosion;[2-4] (b) treated by radiation for benign breast disease;[5] or (c) subjected to repeated x-ray fluoroscopy of the chest in connection with treatment for tuberculosis,[6-10] all suffered a significantly higher incidence of breast cancer in later years than did comparable groups of women considered as controls. Although the amount of radiation exposure in these series of women was many times greater than that encountered in mammography, a National Academy of Sciences review indicated (and we concur) that one must assume a linear dose-response relationship on the basis of present evidence and in the absence of any clear information to the contrary.[11] This means that there is no absolutely safe dose and that, in the case of breast cancer induced by x-rays, the number of cases resulting from the exposure will be simply proportional to

the number of years lived after exposure to a certain quantity of radiation, with some minimum latent period. The National Academy of Sciences report[11] estimated that 6 extra cases of breast cancer are induced per million per year rad after a 10 year minimum latent period."

Arthur Upton, speaking for himself and other leading radiation-biologists appointed by the National Cancer Institute to reexamine the matter, reaffirmed on 19 July 1976 at the National Cancer Institute that linear extrapolation (and no "threshold") should continue as the basis for estimating risk.[12] Incidentally, at least some of the references cited by Sickles do not deny linear extrapolation but merely question whether it has been "conclusively" proved. The evidence both in the 1972 report[11] and subsequently assembled by Upton[12] clearly favors linear extrapolation and no "threshold."

In view of the above-cited evidence and interpretation of it, is it not prudent to assume mammography will induce some breast cancer rather than wait 10 to 30 years for "conclusive proof" among millions of women?

Sickles further expresses a "hope" that the nationwide Breast Cancer Demonstration Detection Project (BCDDP) will result in information as to, among other things, ". . . whether or not there are significant long-term radiation risks."

Unfortunately the BCDDP was not designed to discover, and will not yield, this information. Radiation-induced breast cancer, according to all human exposures studied thus far, begins to appear only after about a ten-year latent period. The BCDDP was designed to include five years of periodic mammography (and other) examinations, and an additional five years of observation. Such a design obviously cannot show "whether or not there are significant long-term radiation risks." Even if the design were altered now, simply to extend the period of observation into the time when radiation-induced breast cancer would be expected to occur, there is presently no control group for comparison. The women coming to the BCDDP constitute a unique group of volunteers, all of whom have been receiving mammography. In the absence of any data showing that radiation-induced breast cancers are pathologically or otherwise unique, and in the absence of a control group, it is difficult to see how any conclusion could be drawn about radiation-induced breast cancer from the BCDDP experience presently underway.

The second main point advanced by Sickles is that we make "no allowance . . . for improvements in mammographic equipment, technique and knowledge that have accrued in the greater than ten-year interval since the HIP (Health Insurance Plan of Greater New York) study mammograms were taken." He then cites certain data from the BCDDP as evidence of this improvement.

The fact "that a third of the breast cancer so far detected [in the BCDDP] has been in women under age 50, and that 45 percent of this cancer was detected by mammography alone" is irrelevant to the important issue of whether current mammography is finding breast cancer in women whose lives will be saved. The fact that a third of the breast cancer detected has been in women under 50 reflects mainly that about half of the women screened have been under 50; if only a fourth of those screened had been under 50 a smaller proportion of the cases found would have been under 50; and if three fourths of those screened had been under 50, a larger proportion would have been under 50. Conclusions about the benefits of mammography cannot be drawn from such proportions, or from the 45 percent figure mentioned by Sickles.

The only scientific approach I can see to ascertaining whether current mammography will disclose breast cancer in women under 50 whose lives can thereby be saved is to conduct a randomized clinical trial which might contradict the HIP data. As medical technology advances and brings greater potential for harm as well as good, the randomized clinical trial will become increasingly important as a means of ascertaining risk/benefit. If mammography technique has advanced to the point where women under 50 who receive mammography routinely do have a substantially better chance of avoiding death from breast cancer than women who do not receive it, that should certainly be established by proper study. The HIP study did not show any such benefit, and that is the only controlled trial to date.

I agree with Sickles' suggestions numbered 1, 2 and 4. I would hope he might change his view on 3. With the available evidence and prudent interpretation of it indicating a risk of radiation-induced breast cancer from mammography; with all the available evidence (the HIP study being the only controlled study) showing no measurable mortality benefit to women under 50; with the BCDDP not designed (and not claimed by its

sponsors) to yield risk/benefit data—why continue routine mammography screening at present for women under 50?

As a long-time and continuing enthusiast for early breast cancer detection, using all appropriate modalities, my preference would be to design and conduct appropriate studies before exposing women under 50 to the risk of radiation-induced breast cancer without clear-cut evidence of benefit.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Acupuncture and Heroin Detoxification

To the Editor: I read with interest the article, "Outpatient Heroin Detoxification with Acupuncture and Staplepuncture" in the September issue (Tenant FS: West J Med 125:191-194, Sep 1976).

In Dr. Wen's original study on the treatment of drug addiction with acupuncture,[1] he had to use electrical stimulation as often as four times per day during the first few days of detoxification. In order to scientifically evaluate the efficacy of acupuncture, one would either have to develop the facilities to treat the addicts that frequently or else have portable electrical stimulators available for the patients to use at home.

Also before one labels acupuncture as just another placebo, one should investigate the Chinese neurophysiological research papers on acupuncture.[2,3]

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More on Physician's Assistants

To the Editor: In the October issue is a letter by Daryl T. Kubotsu [Kubotsu DT: In support of physician's assistants. West J Med 125:329-330, Oct 1976] supporting the concept of physician's assistants (PA).

There is no argument as to the level of training or the mental integrity of the people who are becoming physician's assistants. We, as physicians, realize that physician's assistant programs are good, that the training is concentrated and that the majority of the people who take the course do very well. We appreciate also that they are alert, have confidence in themselves and can do the work very well.

The problem that has arisen in Southern California, as in other areas, is that many of the people working as physician's assistants have begun to think of themselves as doctors. Since the job that they have taken on partly is examining patients in a doctor's office, they themselves are sometimes giving the impression to patients that they are physicians and not physician's assistants in the form of "like a nurse." A week ago I received a call from a medical clinic here in the Fullerton area and the clerk in the clinic told me that the doctor wanted to talk to me. A male voice came on the line and the person stated that he was a doctor. I told him that I had not heard of a new doctor in that particular area. He responded "I am not a doctor, I am a PA but the nurses like to call me 'doctor.'" The physician's assistant himself had said "This is Dr. X" when he answered the phone and then later said that the nurses liked to call him "doctor."

It is no secret that several industrial clinics are using PA's for night and weekend call. I have had multiple complaints from patients stating that they went to an industrial medical clinic at night and were examined by "some guy that thought he was a doctor." Industrial medical clinics are charging industrial insurance companies physician's fees for work that physician's assistants do at night or on weekend call. There are several malpractice suits going on right now involving physician's assistants. Physician's assistants have injured patients, particularly in cutting off casts.

In several instances there has been disruption of an office practice because a physician's assistant will not take orders from the senior nurse in the office and feels that he is superior to the nurse in charge of office management. The physician's assistant concept sounds good on paper but many problems have come up—and there will be more problems as long as PA's do not distinguish themselves from physicians.

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Secondary Prevention in Alcoholism

To the Editor: Whether one is considering tuberculosis, cancer, syphilis or alcoholism, early diagnosis as a means of improving the chances of successful therapy and the likelihood of salvage makes sense. Once therapy for a common serious illness has become feasible, mass efforts often have been made to apply such therapy to afflicted persons. Once there were "chestmobiles" and blood serology teams to diagnose tuberculosis and syphilis as public health measures spread across the land. Now it may be reasonable to initiate mass education and screening programs for early diagnosis of alcoholism so that therapy can begin before extensive organ damage, advanced addiction and episodes of alcohol related violence occur.

Why has there been a reluctance by the medical profession to apply aggressive measures of diagnosis and therapy in alcoholism? Reasons include: (1) nonexistent to inadequate alcoholism education for most currently practicing physicians during medical school and postgraduate training days, (2) uncertainty as to appropriate therapy, (3) exposure to poor success rates—many physicians have never seen a successful alcoholism treatment program and (4) physicians' own alcohol use or abuse.

How should we proceed toward early case finding? (1) Every physician-patient (teenager and older) encounter should include observations directed toward the possibility of alcohol problems. (2) A high index of physician suspicion of the role of alcohol in many conditions should be cultivated. Problems of hepatomegaly, fatty liver, gastritis, ulcer disease, anemia, gastrointestinal bleeding, hypoglycemia, pneumonia, hyperuricemia, burns, fractures, labile hypertension, pancreatitis, seizures, hypertriglyceridemia, anxiety, depression and tremor, as well as suicide attempts and assault and accident victims and perpetrators, all have a high association with alcohol abuse. Alcoholism has replaced syphilis as the great protean imitator. (3) Pilot programs of routine blood alcohol analyses on adult hospital admissions should be done, with subsequent application to any groups shown to have a high benefit-cost ratio. (4) Drunk driving arrests in which a blood alcohol level in excess of 0.1 percent is found should lead to a consideration of alcohol abuse or alcoholism. (5) Lawyers and judges should be made acutely aware of the frequent alcohol tie with marital breakups and violent behavior. (6) Probation officers should be recognized as excellent alcohol abuse case finders. (7) Personnel supervisors noting tardiness, absenteeism and other features of troubled employees could be very helpful. (8) Requiring an alcohol-drug history upon registration for health insurance could be useful. (9) Diagnostic tests for alcoholism, such as an "alcohol tolerance test," could be developed and applied.

Every person in a position of responsibility should seek out an alcohol cause/effect underlying any of these clues. When an alcohol problem is discovered early, the attitude of the patient should be one of gratitude similar to a person with tuberculosis whose case is arrested before his family is infected. All alcoholism patients should be directed into the best available treatment programs, by whatever means is necessary, since the public health is at stake.

This aggressive approach to diagnosis may err on the side of overdiagnosis. Concern for a fine differentiation between alcoholism, alcohol abuse or "problem drinking" should be ignored. Since alcoholism therapy is noninvasive, with a negligible potential for iatrogenic harm, overdiagnosis should not be feared and may prove to be helpful preventive medicine. The physician must assure that treatment for the *alcoholism itself* is given in addition to treatment for whatever other disease may be diagnosed. Treating the pancreatitis and not the alcoholism is of little value.

The total American societal change in attitudes on alcoholism and alcohol abuse from negative, repulsive and punitive to positive, aggressive and redemptive is well on its way. Incredibly, the medical profession has lagged instead of leading. It is to be hoped that this will change.

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Arbitration Agreements

To the Editor: This is in response to the letter by Dr. Edward Bordin in the November issue, in which he comments on my recent article on arbitration [Butler JR Jr: Arbitration agreements and your malpractice coverage (Informed Opinion). West J Med 125:253-258, Sep 1976].

In this age of increasing socialization it may strike some as amazing that physicians still have

a choice as to whether or not they will render their services. Many physicians and even attorneys have raised the problem posed by Dr. Bordin and wondered whether arbitration agreements are valid under any circumstances, much less when they are offered on a "take-it-or-leave-it" basis.

The *Tunkl* decision involved an outrageously bad factual situation which should never have reached the courts. In that case, a physician in the UCLA Medical Center Emergency Room refused to admit or treat any patient unless he executed a document *contracting away his right to sue under any circumstances.* This was not an arbitration agreement. It was a complete waiver of any legal right to redress for malpractice. The *Tunkl* court found such an outrageous contract to be void as against public policy.

In 1964, the California Supreme Court upheld the Ross-Loos arbitration agreement against an attack based upon the *Tunkl* case which argued the contract was a contract of adhesion and unconscionable. In *Doyle v. Giuliucci,* the California Supreme Court stated that the *Tunkl* case had no application to the Ross-Loos binding arbitration agreement. It distinguished the complete waiver of all right to legal redress in *Tunkl* from a mere selection of forum where disputes would be settled.

Then, in August, 1976, the California Supreme Court again considered binding arbitration agreements. This time a challenge was made to Kaiser Foundation Hospitals' agreement. If there was any question in skeptics' minds after that *Giuliucci* decision, the case of *Madden v. Kaiser Foundation Hospitals* should be dispositive once and for all of concerns such as those voiced by Dr. Bordin. The *Tunkl* case was specifically cited by the court and rejected as having no application in the context of binding arbitration agreements. In relevant part, the California Supreme Court stated as follows:

> The concept that a contract of adhesion should be interpreted and enforced differently from an ordinary contract has evolved from cases which have involved contractual provisions drafted and imposed by a party enjoying superior bargaining strength—provisions which unexpectedly and often unconscionably limit the obligations and liability of the party drafting the contract. [Citations omitted.] *The present case resembles those precedents only in that the members were offered the Kaiser plan on a "take it or leave it" basis without opportunity for individual bargaining.* The Kaiser contract, however, lacks those oppressive features which have characterized the contracts adjudicated in the prior decisions. . . .
>
> In many cases of adhesion contracts, the weaker party lacks not only the opportunity to bargain but also any realistic opportunity to look elsewhere for a more favorable contract; he must either adhere to the standardized agreement or forego the needed service. . . . [Citing *Tunkl.*]
>
> *Finally, in all prior contract of adhesion cases, the courts have concerned themselves with weighted contractual provisions which served to limit the obligations or liability of the stronger party. The arbitration amendment, by way of contrast, bears equally on Kaiser and the members.* It does not detract from Kaiser's duty to use reasonable care in treating patients, nor limit its liability for breach of this duty, but *merely substitutes one forum for another.* [Citation omitted.]
>
> Although plaintiff asserts that the arbitration amendment promotes Kaiser's interest to the disadvantage of the members enrolled under the Kaiser plan, she *overlooks the benefits of the arbitral forum.* The speed and economy of arbitration, in contrast to the expense and delay of jury trial, could prove helpful to all parties; the simplified procedures and relaxed rules of evidence in arbitration may aid an injured plaintiff in presenting his case. Plaintiffs with less serious injuries, who cannot afford the high litigation expenses of court or jury trial, disproportionate to the amount of their claim, will benefit especially from the simplicity and economy of arbitration; that procedure could facilitate the adjudication of minor malpractice claims which cannot economically be resolved in a judicial forum. Thus plaintiff's charge that the board surrendered the members' rights to jury trial without receiving an adequate quid pro quo must fail. Moreover, to the extent that arbitration reduces Kaiser's litigation expense, it may enable Kaiser to offer medical care to members at rates lower than otherwise would be the case.

In the *Madden v. Kaiser Foundation Hospitals* decision, the California Supreme Court specifically upheld a binding arbitration agreement offered "on a 'take it or leave it' basis, without the opportunity for individual bargaining." The Court found a key element lacking which was present in *all* other contract of adhesion cases, namely, a contract of adhesion bears oppessively on one party, while limiting the obligations or liabilities of the stronger party. The Court found that arbitration acts to both parties' advantage. These advantages of arbitration, noted by the California Supreme Court as preventing an arbitration agreement from being a contract of adhesion, are discussed in much greater detail in this author's article cited by the California Supreme Court in *Madden.* The article was entitled "Arbitration: An Answer to the Medical Malpractice Crisis" and appeared in the September/October 1975 issue of the *Beverly Hills Bar Journal.*

The only caveat, and one worth noting, is the suggestion that a patient must have a realistic opportunity to look elsewhere for a more favorable arrangement. That will not be true in emergencies.

If someone were to offer the "voluntary" CMA arbitration agreement to a patient bleeding to death on the operating table, I sincerely doubt that any court would find such an agreement to be voluntarily executed. Such a patient would not have a realistic opportunity to look elsewhere. However, in all *non*emergency situations, you can simply hand the patient the yellow pages and tell him to go elsewhere if he does not want to sign a binding arbitration agreement.

Finally, it should be noted that the *Giuliucci* and *Madden* decisions were decided under the general California law as it existed prior to and without the additional benefit of new California Code of Civil Procedure Section 1295, as adopted by the Keene bill. If anything, that section further enhances the enforceability of binding arbitration agreements and is directly responsive to Dr. Bordin's quoted language on the *Tunkl* case. The new statute provides as follows:

> Any contract for medical services which contains a provision for arbitration of any dispute as to [medical malpractice] . . . is *not a contract of adhesion nor unconscionable nor otherwise improper* where it complies with subdivisions a, b, and c, of this section.

Subdivisions a, b, and c, of the new law are very simple to comply with. Once compliance is made, the enforceability of the agreement is guaranteed by two California Supreme Court decisions directly in point and a formal legislative enactment. What could be more definitive?

I hasten to add that the California Medical Association-California Hospital Association arbitration agreement is a thoughtful, well-prepared document. I believe any such document prepared for general use and without specific advice of counsel must, however, be designed to satisfy the lowest common denominator. That means many physicians using the CMA-CHA package will have an unnecessarily limited or overcautious document when the advantages to be gained by a custom-tailored agreement are far greater.

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* * *

To the Editor: Bordin's comments in the November issue [Bordin EH: Arbitration agreements (Correspondence). West J Med 125:400, Nov 1976] are worthy of some rebuttal. He is comparing apples to oranges in trying to make parallels between arbitration agreements and exculpatory agreements.

Bordin implies that there has not been a test case on arbitration that has withstood the appeals system. *Madden vs. Kaiser* is a most recent decision at the California Supreme Court level supporting both the concept of arbitration in medical malpractice and the authority of the employees' association that Madden belonged to to negotiate an arbitration agreement on her behalf without her express consent. The language of the majority decision expresses the thought that the day of judicial hostility toward arbitration in medical malpractice is over and that attempts to resurrect those days should not occur. The majority decision also pointed out that the patient's references against arbitration were both old and from other states. In the minority decision the lone dissenter quoted only old material and incidentally mainly quoted articles he himself had written.

Bordin's quotes from *Tunkl* are attempts to resurrect the days of judicial hostility toward arbitration in medical malpractice. It would be interesting to know if Bordin is or is not using arbitration agreements at all.

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Refer to: Mandell P, Raih T, Taylor LW: A history of orthopedics in San Francisco and the West (Medicine in American History). West J Med 125:502-508, Dec 1976

A History of Orthopedics in San Francisco and the West

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The unique development of early medical specialization in the West can be traced to California's geography and economic development. Such early specialization produced men with orthopedic inclinations. Early orthopedists founded the first medical school and the first modern teaching hospital, helped to found Stanford's Lane Medical Library and made the first use of x-rays in the West. In addition many of these orthopedists were prominent in the political and social activities of the time.

EARLY MEDICINE in California centered about the system of missions set up from San Diego to San Francisco by the first Spanish settlers. These missions were not only spiritual but also medical centers for the surrounding agricultural communities. Early in its history California medicine developed a tradition of referring cases from the sparsely populated farmlands to a central area. This tradition was to be important in later years for the development of medical specialization including orthopedics in the West.[1]

Before the gold rush California was isolated. Few people could muster the time and money necessary to make the arduous journey over the deserts, mountains or vast ocean stretches. But those who did arrive in California were very much interested in medicine and their health, and they wasted little time in telling the world of their newly discovered land. The great selling point of California was its healthful climate which the scientists of the day had computed to be one of the finest in the world. A year before the gold rush a San Francisco physician wrote:[2]

> Nor is sickness that scourge of humanity here to harass and hinder us in our pursuits. The general salubrity of California has justly become a proverb. The surgeons of San Francisco have remarked that wounds heal here with astounding rapidity owing, it is supposed in great measure, to the extreme purity of the atmosphere.

Despite its great health claims San Francisco was able to attract less than 5,000 people by 1848. Yet within the next four years the Bay Area became one of the great commercial centers of the world following the discovery of gold in the Sierra Nevada foothills. With this discovery a major revolution in San Francisco medicine occurred. Hundreds, perhaps even thousands of doctors poured into California seeking riches first in the gold fields and then in medicine, healing those who had struck it rich. A month after the discovery of gold there were about 30 physicians set up in tents within 100 yards of Sutter's mill. And it is easy to understand why when one recalls that the charge for cholecystectomies was $1,500

This paper is based on material presented as an exhibit at the 1975 meeting of the American Academy of Orthopaedic Surgeons and on material presented in 1975 at a University of California, San Francisco, Orthopedic Grand Rounds.

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Figure 1.—Elias Samuel Cooper, founder of the first medical school in the West and one of the West's first joint surgeons.

apiece, with other surgical procedures similarly priced. Many of the "doctors" who came to town were poorly trained and most were persons who had been driven from their eastern or European cities to San Francisco. The ratio of physicians to patients quickly grew to five times the national average and has remained elevated to this day.[3] This influx of doctors naturally sparked competition and violent literary attacks by one group of physicians upon another. In 1850 one doctor wrote "We physicians are at the most ruinous discount . . . held in so low repute that many a worthy physician studiously conceals his title." Another doctor of the period observed, "We live in continual war with each other—an internecine war, murderous and suicidal."[4]

Amid this surfeit of doctors, San Francisco's earliest orthopedic ancestor, Elias Samuel Cooper, felt compelled to open the first medical school in the West. Dr. Cooper (see Figure 1) was an aggressive man who, according to Emmet Rixford, "could not be accused of hiding his light under a bushel, for he advertised widely his ophthalmic and orthopaedic dispensory in the several score of newspapers of the mining districts."[5] Dr. Cooper's efforts to increase the number of physicians in San Francisco were not met with great enthusiasm. One member of San Francisco's medical community greeted the introduction of Cooper's school with these words:

> A medical college is not needed here. There is no fund for the endowment of the college, and there are no students to attend the lectures, and there are no capable physicians who have the leisure and philanthropy to deliver lectures gratis. . . . We hope our Atlantic brethren will not be deceived. The Pacific Medical College is now a legitimized sham—a legal humbug—a chartered advertising medium for the man (who founded it).[6]

Cooper's orthopedic credentials include contributions on knee joint surgical procedures. He apparently researched this subject in some detail and was said to have originated a totally new theory for such operations. Cooper was also the first San Francisco surgeon to publish on an orthopedic topic when he wrote "A New Method of Treating Long Standing Dislocations of the Scapulo-Clavicular Articulation" in 1861.[7]

Dr. Cooper's orthopedic contemporaries include Augustus Jesse Bowie who was known throughout the city for his conversational powers. It was said that so legend were Dr. Bowie's talents that "sometimes men took to bed in order to have the pleasure of the doctor's visit."[8] Bowie's formal training ceased when he was 13. Thereafter he apprenticed himself to a surgeon in Baltimore and arrived in San Francisco in 1849 aboard one of the first United States Navy steam powered ships to join east and west coasts. In addition he became the first surgeon at St. Mary's Hospital when it opened in 1861. Indeed, according to an article by E. S. Cooper, Dr. Bowie's fame as a bone surgeon was won at St. Mary's Hospital. Cooper[9] noted that Bowie:

> had a number of cases of operations for Pseudoarthrosis, and, with one exception, had entire success. This is more than can be said of the Hospital Surgeons of London and Paris, who not only fail in removing the deformity, but frequently lose their patients. The latter circumstance seldom or never occurs in this city.
>
> It cannot be denied that San Francisco leads the surgical world in the success of operations

Figure 2.—Harry Mitchell Sherman in 1918, the first true orthopedist in the West.

> upon the bones. So much is this the case, that Surgeons abroad are slow to believe half of what is truly told them, in regard to our successfully "playing with bones and joints," . . . as they denominate it.

As California developed, its agriculture also grew. Most of the produce moved to market on the two great rivers that drained the central valleys. Since these rivers flow into San Francisco Bay, Bay Area cities became great agricultural marketing centers. But the same barges that brought produce to San Francisco also brought patients from the outlying agricultural areas. These rural patients gave the doctors of San Francisco a far greater patient area than just the city itself. More hospitals and more physicians were thereby supported in San Francisco than in other American cities of comparable size. It is said that many San Francisco physicians did not have a single patient from within the city limits.[10]

Naturally this influx of patients led to the early development of specialists in San Francisco. Cooper and Bowie might have been considered early bone specialists but the first physician that we would unmistakenly recognize as an orthopedist moved west in 1885. Harry Mitchell Sherman (see Figure 2) was born in Rhode Island just five years after the gold rush. He trained in New England as did many of his distinguished successors in the West. Only a year after his arrival Sherman developed an interest in crippled children. He became the surgeon at Children's Hospital and before he died in 1921 he had made Children's Hospital the orthopedic center of the West. One of Sherman's students recalled that Sherman's manner was that of a grande seignior —formal, courteous and punctilious. But Sherman seems to have had his less formal moments as well. One of his favorite pastimes at lunch was taking target practice with his .44 caliber pistol in his downtown office.

By 1900 Sherman was such a respected member of the orthopedic community that he was elected president of the American Orthopaedic Association. That same year his future partner, James T. Watkins, while touring the orthopedic centers of Europe was amazed to learn that whenever he told his hosts that he intended to practice in San Francisco they would reply "Oh yes, Sherman is in San Francisco."[11]

Sherman was interested in hospital construction and experimented with different colored tiles and drapes in the operating room. He finally hit upon green, a color still used today. Sherman was one of the first men in San Francisco to recognize the importance of a university teaching hospital after the model of Johns Hopkins. His opportunity for this endeavor came when the 1906 earthquake and fire devastated the city and most of its hospitals. Sherman and others converted part of the University of California Medical School to a teaching hospital and Sherman supplied not only the first patient to the new hospital but also the first bed.

Not only was Sherman the first internationally recognized orthopedist in the Bay Area but he was a man great enough to admit his mistakes in public. He once published an article detailing the reexploration of a patient in whom he had left a sponge seven years before.[12] Even in his time such written candor was rare.

Sherman's longtime partner was James T. Watkins, who was born in Baltimore but passed much of his years in California. His grandfather, Commodore James T. Watkins, had carried the news of California's admission to the Union around the Horn. While growing up Watkins had the pleasure of meeting many of his father's famous friends, including Mark Twain and Bret Harte.

After moving back east to attend the University of Virginia young Watkins obtained a medical

Figure 3.—The first medical use of x-rays in the West at the University of California, Berkeley, Physics Laboratory.

degree from Columbia in 1894 and then spent three years in New York. For an additional three years he studied orthopedics at various European centers with Hoffa, Lorenz and Lange.

In 1902 James T. Watkins, now a bright young physician, returned to San Francisco and became the first on record to openly challenge Harry Mitchell Sherman's medical judgment. After two months of stony silence Dr. Sherman quietly asked young Watkins to join him in practice.

Dr. Watkins became an outstanding community and national figure. Immediately after the 1906 earthquake he became the city's health officer. He was a charter member of the American College of Surgeons and helped organize the San Francisco Orthopaedic Club in 1920 and the Western Orthopaedic Association. As 41st President of the American Orthopaedic Association in 1927 Watkins courted the orthopedic world by hosting the annual meeting at Yosemite Valley. In his presidential address he stressed the compatibility between science and religion. When Watkins died in 1934 the orthopedists of the West had lost their leader and San Francisco had lost a great citizen.

During the period when Sherman and Watkins were working and studying in San Francisco other innovative men were also beginning a grand tradition of orthopedic research in California. A. W. Morton was one such man. In 1903 he reported his successful results in treating a long-standing, infected, tibial nonunion by implanting a dog bone still attached by a pedicle to the dog. Dog and man were then encased in plaster for five weeks, and according to Morton the patient suffered very little pain except for the first two or three postoperative days when the dog attempted to move.[13]

A far more important experiment for orthopedics was conducted at Berkeley in February 1896 (see Figure 3). A 13-year-old boy had received a gunshot wound to his hand and his surgeon had been unable to locate the bullet by probing. The boy was then taken to the University of California physics laboratory where his hand was strapped to a photographic plate and held there for 90 minutes of x-ray exposure. The resulting picture was of poor quality and the boy was then reexposed for two and a half hours before a good picture was obtained. This experiment was the first medical use of x-rays in the West.[14]

Around the turn of the century several men who made contributions to Bay Area orthopedics were coming to the front. Emmet Rixford for example was a surgeon with orthopedic leanings who had graduated from Cooper's medical college. He had a strong interest in engineering and his early publications dealt with green stick fractures, torsion fractures and other afflictions of bones and joints. Rixford was instrumental in setting up Stanford's Lane Medical Library. His love of books was so great that during the fire and earthquake of 1906 Rixford buried some of his books to prevent their destruction. Some of these books are still housed in the Lane Library.

Sam Hunkin came to California as a sailor from Cornwall. He worked his way through college firing a steamboat on Lake Tahoe. He enrolled at Toland Medical School and upon graduation in 1890 he became an assistant to Harry Sherman at Children's Hospital.

Hunkin was a swift and skillful surgeon, who spent about 30 minutes doing a laminectomy. He was a prolific writer, and as early as 1912 he reported 12 successes in 12 attempts at treating femoral neck fractures with a large silver plated nail.

Figure 4.—Leonard Wheeler Ely, first professor of orthopedics at Stanford University.

Hunkin was a colorful figure who could be seen making his rounds from hospital to hospital in a chauffeur-driven limousine. He had what might be termed a keen eye for the ladies—aided, of course, by his smooth style and impeccable dress. In his later years it appears that Hunkin dropped into obscurity as if shunned by the medical society of the day. His personal life apparently did not meet the standards expected of a physician. Except for his obituary and his numerous publications, there is little evidence that this man practiced orthopedic surgery in San Francisco for nearly 40 years.

Leonard Wheeler Ely (see Figure 4) was born and educated in New York. He began his practice in the East and then started his trek west, settling for a time in Denver where he developed interest in joint tuberculosis.

In 1913 he met and married the daughter of Ray Lyman Wilbur, the president of Stanford University, and in 1914 he became the first professor of orthopedics at Stanford. From that time until he retired in 1934 he published more than 100 articles and three textbooks. Throughout his writings and teachings Dr. Ely worked to place the knowledge of bones and joints on a firm scientific basis.

Although Ely had served in World War I he felt compelled to contribute to the war effort in World War II at the age of 74. When he was not accepted into the military service as a physician he went to work in a shipyard. However, the task proved too much for him and he died quietly in his sleep.

Bay Area orthopedics took a turn for the better in 1923 when Shriners Hospital was established. Its first chief was Walter I. Baldwin who was succeeded at Shriners by Edward (Ned) Bull in 1927. Bull was so compulsive about his lectures that he often stayed up until three in the morning preparing one, only to sleep right through it. While he was chief at Shriners (1927-1931) he loved to teach but he loved to talk even more and many a physician avoided being cornered by Dr. Bull unless they had an hour or so to spare.

Sylvan Haas was the next Shriners chief. He did his internship at Lane Hospital and then spent one year in Europe studying pathology. During World War I he was instrumental in organizing what later became the Armed Forces Institute of Pathology. His early interest in pathology primarily dealt with bone physiology and disease and set the ground work for his research. He wrote a great deal, was a tireless researcher and published more than 50 articles during his lifetime. Dr. Haas was one of the first American authors to study the epiphysis in detail. He was an early pioneer in the treatment of leg length discrepancy by epiphysiodesis.

Several of Haas' contemporaries also contributed to Bay Area orthopedics. These men include George McChesney, Lionel Prince, J. Judson Sale, John Loutzenheiser and General Norman T. Kirk, who became Surgeon General of the Army. Yet it remained for LeRoy Abbott to make the Bay Area a major center for orthopedic training.

Abbott was born in Minnesota but graduated from the University of California Medical School in 1914. He then trained in Boston where he had a chance to observe firsthand how the finest orthopedic training in the country was then carried out. During World War I Abbott was fortunate enough to meet some of the great British orthopedists, including Sir. Robert Jones and Sir Harold Stiles. In fact, after the war Abbott became Stiles' first American resident.

His training completed, Abbott launched his academic career in Michigan and then Missouri before returning to the University of California in 1930. There he found his work cut out for him as he assumed the chairmanship of a division with

no recent leader, practically no funds and a clinical staff of only 12. There were no salaries paid to him or his staff and precious few beds at the university and county hospitals. From this shaky beginning Abbott was to fashion a formidable orthopedic department. He did it by his own great teaching ability and by his knack for keeping people busy and productive enough so that they had little time to squabble among themselves. Some of Abbott's Bay Area colleagues such as Ralph Soto-Hall, Donald King, Keene Haldeman and Merrill Mensor are still contributing to orthopedics today.

Abbott had the sagacity and luck to surround himself with brilliant men. In 1931 he coaxed Dr. Frederick Bost to join him after the completion of his training at Harvard. Bost became chief of San Francisco [General] Hospital where he was recognized by his students as a great, if somewhat hard-driving, teacher. A man of short stature, Bost used to back up, stand on his toes and rest his heels against a wall when lecturing on rounds. He became chief at Shriners Hospital and is the only Bay Area orthopedist to have been president of the American Academy of Orthopaedic Surgeons.

About the same time that Bost joined his department, Abbott was able to get J. B. de C. M. Saunders to work in orthopedics. Saunders was apparently hired in Scotland by the chief of the University of California anatomy department as a half-time anatomist and half-time surgeon, but when Dr. Saunders arrived in San Francisco the surgery salary was not available and Abbott seized the opportunity to give Saunders an appointment in orthopedics.[15]

Dr. Abbott was never one to let a good opportunity go to waste or to use time foolishly. In 1947, he had need of an orthopedist for the Ft. Miley Veterans Administration Hospital. One day he was administering the anatomy portion of the Orthopaedic Board Examination to Dr. Floyd Jergesen, a man whom Abbott had met and talked with before. Abbott offered him the job at Ft. Miley on the spot, and while they were discussing the details, the bell rang without a single anatomical question having been asked.[16]

Abbott also called upon some of his promising residents to fill teaching and research duties in his department—men such as Verne Inman and Gerald Gill. Inman combined his strong interests in engineering with those in medicine. He taught anatomy for a time before beginning his orthopedic training. In 1940 Inman received a grant from The National Foundation for Infantile Paralysis to study the anatomy and physiology of skeletal movements. Along with Abbott and Saunders he produced a classic study on shoulder movements. The experiences gained in this initial prewar study were to prove invaluable to Dr. Inman, as World War II brought an increased need for prosthetic devices. When the manufacturers of these devices found that they did not understand what they were trying to replace, Drs. Inman, Saunders and Abbott produced papers on the major determinants of gait, the action of the ankle joint, referred pain from skeletal structures and the biomechanics of hip joint motion. These studies have become part of the foundation of modern orthopedics and are a far cry from the early Bay Area experiments of Morton and his dog bone graft.

In addition to surrounding himself with great men at the University of California, Abbott also expanded his residency program to include hospitals throughout the east and west bay areas. With the incorporation of the East Bay hospitals Abbott had a chance to expose his residents to the teaching talents of such men as Harold Hitchcock, Leonard Barnard and Douglas Toffelmier.

By 1957 when Abbott retired, his goal of achieving a great orthopedic service in the Bay Area had been achieved. From a department with no leader, no funds and few teachers Abbott had fashioned a department of national prominence.

Conclusion

The orthopedic history of the Bay Area has been remarkably colorful and varied. Its early Spanish heritage began with the mission referral system which led to medical specialization. The gold rush brought in medical entrepreneurs from all over the world whose wisdom helped to found the orthopedics of today. Some of the great social and scientific institutions of the West were founded by, or with the help of, men interested in bone and joint surgery. We have mentioned E. S. Cooper and his medical school—which was to become the medical school of Stanford University. Emmet Rixford helped to establish one of the great medical libraries of the West. Harry Sherman established Children's Hospital as the orthopedic center of the West in its day and put San Francisco on the orthopedic map.

In addition, orthopedists were in the forefront

of much important scientific research in the Bay Area. We have noted that the first x-ray films taken in the West were of a boy with an extremity injury. The first physicians to clearly define how men walk were Bay Area orthopedists, as well.

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Important Medical-Legal Aspects of Immunization

There have been some recent medical-legal developments that I think may cause you grave concern . . . and I would urge you to spend a little more time talking to parents on a child's first visit for immunizing agents. In 1963, in the case of Davis vs. Wyeth, wherein an adult who had participated in a mass Sabin vaccine program in Idaho contracted poliomyelitis, and in which case it was shown that his paralytic disease was vaccine-associated: The first court of jurisdiction found for Wyeth, the defendant, saying that it was well-known that Sabin oral polio vaccine did carry a small risk (1 case in 3 million, or 1 in 5 million, depending on the type of vaccine strain) and that, therefore, this was to be expected . . . The 9th Federal Circuit Court, however, reversed the decision and said that there was an "implied warranty" any time a manufacturer put a product on the market. And even though that manufacturer had fulfilled all the standards of safety testing as required by the government at that time, the manufacturer himself (or his representative) must warn the patients who are receiving these products of the risk.

Seven years later, in 1970, there was an outbreak of natural poliomyelitis in South Texas due to polio type 1. Because of this there was a mass program in the community, and in a public health clinic an 8-month-old child . . . received a feeding of vaccine strain and paralytic poliomyelitis later developed. It was shown conclusively by expert witnesses who studied the virus recovered from the child that the child suffered from natural poliomyelitis and not from the vaccine strain. Yet, the courts found against the manufacturer, Wyeth. They disregarded the expert testimony that the vaccine had nothing to do with the child's paralytic disease, which was naturally acquired, and again brought up this business of the implied warranty.

Now . . . this may sound like it's a long way from your individual practice . . . but to protect ourselves and to be defensive I would suggest to you very strongly that you give the parents a handout on immunizing agents that you're going to use rather routinely . . . You better make sure that your chart reflects that you have talked to the parents about the immunizing agent; and you should also record the child's temperature. And my advice to you is that although there is no contraindication, in my opinion, to use the trivalent oral polio vaccine in a febrile child, I wouldn't use even that in a febrile child now because of some of the medical-legal implications I've seen.

—HENRY G. CRAMBLETT, MD, *Columbus, OH*
Extracted from *Audio-Digest Pediatrics*, Vol. 21, No. 14, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

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What Do We Know About Cancer?

A Bicentennial Perspective

MICHAEL B. SHIMKIN, MD
La Jolla, California

Some Historical Mileposts

WHAT HAS BEEN LEARNED about neoplastic diseases during the past 200 years? Twelve events and subsequent developments can be indicated as historical mileposts. These are illustrated by historical covers from *Cancer Research* or other photographs from that journal's files.

Presented at the Colloquium on the Bicentennial of Medicine in the United States, 1776-1976, National Institutes of Health, Bethesda, May 6-7, 1976.

Reprint requests to: Michael B. Shimkin, MD, Department of Community Medicine, UC, San Diego, School of Medicine, La Jolla, CA 92093.

200 years since the first description of an occupational, environmental cancer (Percival Pott, England, 1775). Shown are Percival Pott and 18th century chimneysweeps.

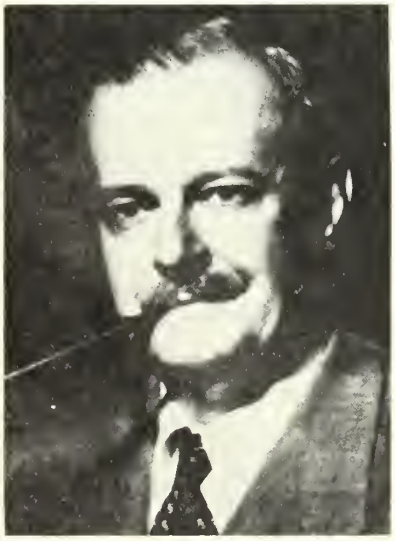
140 years since the first histological studies on cancer (Johannes Müller, Germany, 1838). Johannes Müller is pictured with illustrations of cancer cells.

100 years since the first successful transplantation of cancer in animals (M. Novinsky, Russia, 1876). M. Novinsky and transplanted dog cancers are pictured.

100 years since the introduction of modern surgical procedures for cancer (Theodor Billroth and others, Austria, 1880's).

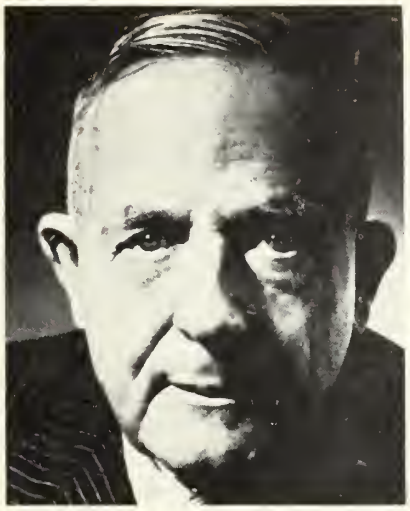
65 years since the discovery of the first virus-induced cancers (Peyton Rous, U.S.A., 1911). The photograph illustrates Rous' work with virus tumors of chickens.

60 years since the first chemically-induced (tar) cancers in animals (K. Yamagiwa, Japan, 1915). Shown are Japanese researchers K. Yamagiwa (right) and K. Ichikawa (left).

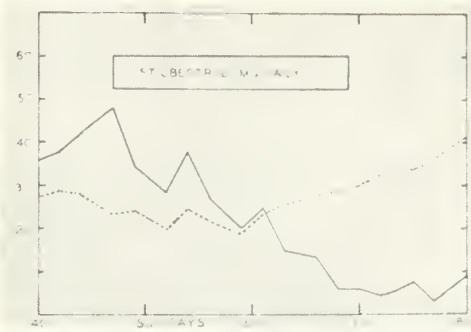


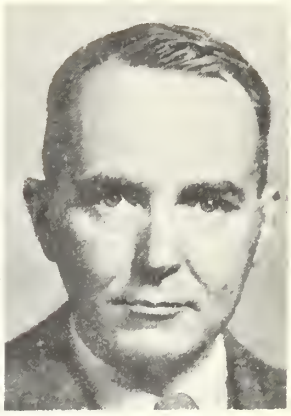
55 years since the initiation of genetic studies of cancer (C. C. Little and others, U.S.A., 1920's).

55 years since modern radiotherapy for cancer (H. Coutard and C. Regaud, France, 1922). Regaud is shown on left and Coutard on right.



50 years since modern biochemistry in cancer (Otto Warburg, Germany, 1926).





35 years since the beginning of modern chemotherapy for cancer (Charles Huggins and others, U.S.A., 1940's). A graph from Huggins' work with chemotherapy of prostatic cancer is shown.

15 years since the modern period of immunology of cancer (George Klein and others, Sweden, 1960). Shown are George and Eva Klein.

10 years since the application of molecular biology to cancer (Howard M. Temin and others, U.S.A., 1960's). D. Baltimore (left) and H. M. Temin (right) are shown.

Scientific progress is achieved by individual investigators, often by several simultaneously, when the accumulated information reaches a critical mass. But of importance equal to the genius and devotion of individual scientists is the program against cancer conceived and developed in the United States. This program was written into law in 1937 and in 1971, as the National Cancer Acts, proclaiming that the cancer problem can and will be solved by scientific research, and committing national treasure toward the goal. And the major stimulant of the program was the American Society for the Control of Cancer created in 1913 and organized as the American Cancer Society in 1944.

What Is Cancer?

Our present knowledge regarding neoplastic diseases can be summarized in five broad statements.

- Cancer is a large group of diseases, characterized by changes in somatic cells that are transmissible to daughter cells.
- The basic cellular change that eventuates in the clinical manifestations of cancer involves the genetic component, the deoxyribonucleic acid moiety, of the nucleus.
- The cancerous change can be triggered by a wide variety of environmental stimuli, including physical, chemical, and viral agents.
- The cancerous process is usually manifested after prolonged repeated exposures to the carcinogenic stimulus, and evolves through a series of changes.
- The cancerous process is influenced by many host factors, including heredity, nutrition and immunologic status.

What Can Be Done Against Cancer?

Knowledge regarding cancer has led to the following practical applications:

- In *prevention,* hundreds of defined environmental carcinogens have been identified. Tobacco smoking, industrial chemicals and ionizing radiation are man-made hazards; aflatoxin is an example of a natural carcinogen. Avoidance or elimination of exposures to carcinogens would prevent a significant proportion of cancers in man.
- In *diagnosis,* pathology remains supreme, with the biopsy being the basis, and microscopic designation of histogenesis, staging and grading leading to the determination of prognosis as well as of diagnosis.
- In *treatment,* surgical operation remains the most definitive approach, aiming at total removal of the cancer. Radiotherapy is curative in cancers responsive to host-tolerated doses and encompassable by the beam. Chemotherapy cures some rapidly-proliferating cancers. Combinations of all three modalities are of increasing importance.
- In *prognosis,* the salvage rate of all patients with cancer approaches 40 percent at five years after treatment. Improvements in salvage for patients with some cancers are insufficient to reverse rising mortality from other cancers.
- Real victory over cancer is still in the future, requiring better application of available knowledge and discoveries of new preventive and therapeutic methods through research.

"Things won are done: joy's soul lies in the doing."—SHAKESPEARE, *Troilus and Cressida, Act I, scene ii, line 313.*

Using Tetracycline in the Treatment of Pustular Acne

The major sales in this country for tetracyclines appear to be for the treatment of pustular acne, at a dosage of 250 mg once a day. For many years . . . we really couldn't see the rationale for employment of such a small amount of antibiotic and we used to say "it's hogwash!" Subsequently, some dermatologists, at least the investigative ones, came up with two rationales. One is that one of the organisms responsible for pustular acne is Coryne bacterium acneformi. This particular type of organism has various lepolytic enzymes that break down sebaceous material. It appears that tetracycline is effective not only against the organism but also in decreasing sterol production, so it appears to work. It is also associated with very little evidence for harm, even when given in chronic dosages.

—MARVIN TURCK, MD, *Seattle*
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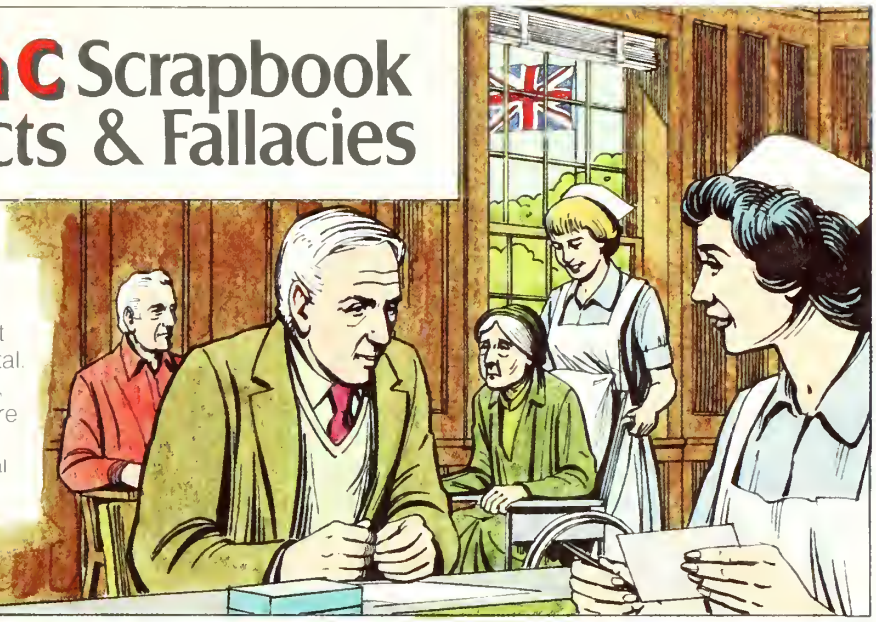
The ALLBEE® with C Scrapbook of Vitamin Facts & Fallacies

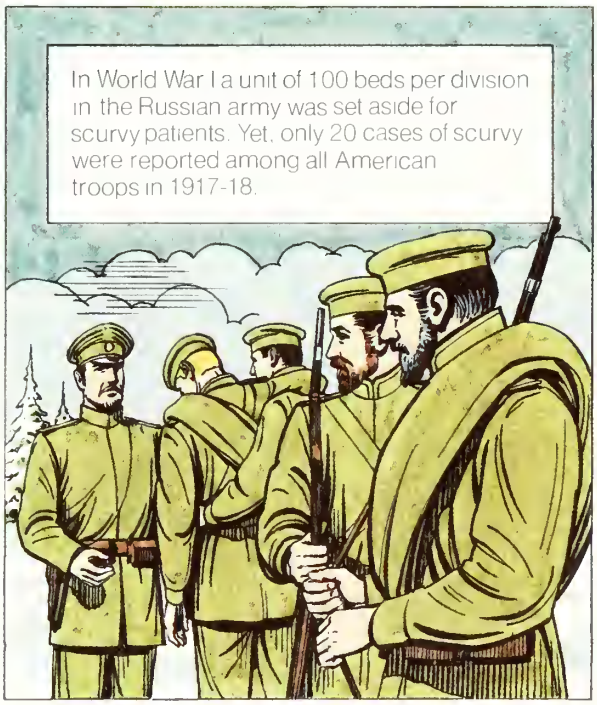


A study conducted among elderly patients in England showed that 41% were deficient in ascorbic acid on admission to the hospital. Even among those living at home and well, or not sufficiently ill for admission, 27% were deficient in ascorbic acid

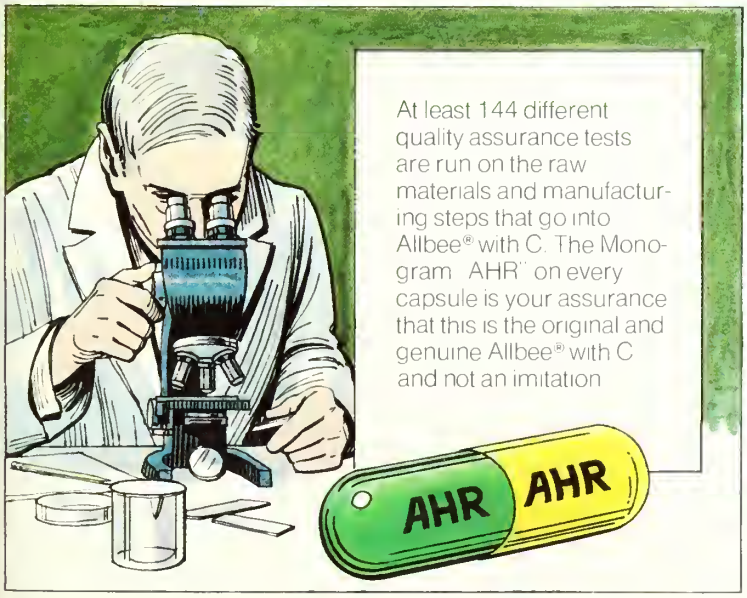
Griffiths, L L, Brocklehurst, J C, MacLean, R et al *Diet in Old Age*, Brit Med J 1 739, 1966

The loss of riboflavin in milk in a glass container exposed to sunlight for two hours may be as high as 95%.

Quick freezing of vegetables is accompanied by very little ascorbic acid loss. But blanching, washing, and prolonged standing at room temperatures results in considerable reduction in Vitamin C content.



In World War I a unit of 100 beds per division in the Russian army was set aside for scurvy patients. Yet, only 20 cases of scurvy were reported among all American troops in 1917-18.



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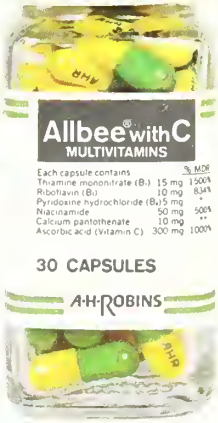

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Brief summary. Contraindicated in patients with glaucoma, renal or hepatic disease, obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy) or a hypersensitivity to any of the ingredients. Blurred vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur at higher dosage levels, rarely at the usual dosage.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

PHYSICIAN'S HANDBOOK—Eighteenth Edition—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Norman J. Sweet, MD, Associate Professor of Medicine, San Francisco General Hospital, University of California, San Francisco; Ernest Jawetz, PhD, MD, Professor and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California, San Francisco; Edward G. Biglieri, MD, Professor of Medicine, Chief of Endocrine Services, San Francisco General Hospital, University of California, San Francisco; and Robert L. Roe, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 754 pages, $8.00.

PHYSIOLOGY—A Clinical Approach—Second Edition—G. R. Kelman, MD, PhD, MRCP(Ed), Professor of Human Physiology, University of Aberdeen; with Chapters 13 and 14 by T. J. Crow, PhD, MRCP(UK), MRC Psych, Head, Division of Psychiatry, MRC Clinical Research Centre, Northwick Park Hospital. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 215 pages, $6.95.

PRACTICAL HAEMATOLOGY—Fifth Edition—J. V. Dacie, MD(Lond), FRCP(Lond), FRC Path, FRS, Professor of Haematology, Royal Postgraduate Medical School, London; and S. M. Lewis, MD (Cape Town), DCP (Lond), FRC Path, Reader in Haematology, Royal Postgraduate Medical School, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 629 pages, $20.00.

RECENT ADVANCES IN PLASTIC SURGERY—Number One—Edited by James Calnan, FRCP, FRCS, Professor of Plastic and Reconstructive Surgery, University of London, Royal Postgraduate Medical School and Hammersmith Hospital, London. Longman Inc., 19 West 44th Street, New York City (10036), 1976. 210 pages, $28.50.

STEDMAN'S MEDICAL DICTIONARY, Illustrated—A Vocabulary of Medicine and Its Allied Sciences, with Pronunciations and Derivations—Twenty-Third Edition (Completely Revised by a Staff of 36 Editors, covering 46 Specialties and Subspecialties). The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD (21202), 1976. 1678 pages, $21.95.

SURGICAL DISORDERS OF THE PERIPHERAL NERVES—Second Edition—Sir Herbert Seddon, CMG, Honorary Consulting Surgeon, Royal National Orthopaedic Hospital, London; Honorary Fellow, Worcester College, Oxford; Sometime Nuffield Professor of Orthopaedic Surgery, Oxford, and Professor of Orthopaedic Surgery, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 336 pages, $39.50.

THORACIC AND CARDIOVASCULAR SURGERY WITH RELATED PATHOLOGY—Third Edition—William W. L. Glenn, MD, Charles W. Ohse Professor of Surgery, Yale University School of Medicine; Chief of Cardiothoracic Surgery, Yale-New Haven Hospital; Averill A. Liebow, MD, Professor and Chairman, Department of Pathology, University of California, San Diego, School of Medicine; Pathologist-in-Chief, University Hospital, San Diego; and Gustaf E. Lindskog, MD, William H. Carmalt Professor of Surgery Emeritus, Yale University School of Medicine, New Haven. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., 292 Madison Avenue, New York City (10017), 1975. 1345 pages, $55.00.

URINARY DIVERSION STOMAS: A Guide for Patients and Nurses—Second Edition—Eileen M. Spraggon, SRN, Stoma Therapist, Department of Urology, Newcastle General Hospital; Foreword by John Swinney, MD, MS, FRCS, Emeritus Professor of Urological Surgery, Newcastle University Hospitals. Longman, Inc., 19 West 44th St., New York City (10036), 1975. 41 pages, $3.25 (softbound).

VENOUS THROMBO-EMBOLIC DISEASE—A Symposium held at the William Robertson Building, University of Edinburgh—Editors: C. Vaughan Ruckley, MB, ChM, FRCSE, Consultant Surgeon, Western General Hospital and Senior Lecturer in Clinical Surgery, University of Edinburgh; and Iain M. C. Macintyre, MB, ChB, FRCSE, Lecturer in Clinical Surgery, University of Edinburgh. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 255 pages, $17.50.

ACUPUNCTURE THERAPY—Current Chinese Practice—Second Edition—Leong T. Tan, MD, practicing urologist, San Francisco; Margaret Y.-C. Tan, MS, Acupuncturist, Acupuncture Research Clinic, University of California, San Francisco; and Ilza Veith, PhD, DMedSc, Professor and Vice Chairman, Department of the History of Health Sciences, University of California, San Francisco. Temple University Press, Philadelphia (19122), 1976. 259 pages, $17.50.

ANTIMICROBIAL DRUG THERAPY—Major Problems in Internal Medicine: Volume VIII—Abraham I. Braude, MD, PhD, Professor of Medicine and Pathology; Chief, Division of Infectious Diseases, University of California, San Diego, School of Medicine; Director of Microbiology, University Hospital, San Diego. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1976. 218 pages, $12.00.

A NEW KIND OF JOY—First Edition—James Haskins. Introduction by Eunice Kennedy Shriver. Doubleday & Company, Inc., 245 Park Avenue, New York, NY (10017), 1976. 115 pages, $7.95.

(Continued on Page 18)

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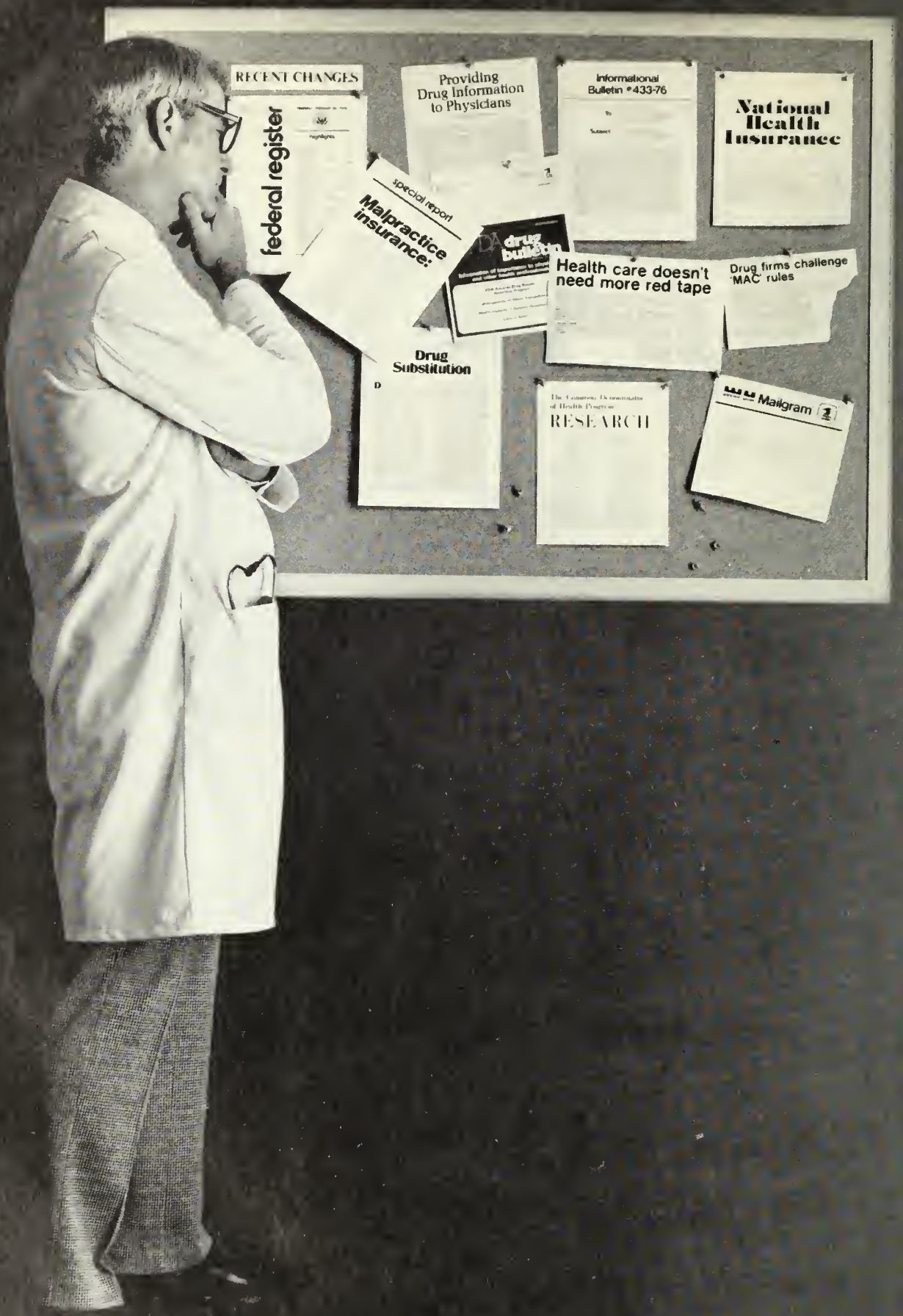
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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

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BOOKS RECEIVED

(Continued from Page 15)

ATLAS OF ANATOMY OF THE HAND—Johan M. F. Landsmeer, Professor of Anatomy and Embryology, University of Leiden. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 349 pages, $55.00.

AUSCULTATION OF THE HEART AND PHONOCARDIOGRAPHY—Second Edition—Aubrey Leatham, MB(Cantab), FRCP, Physician to St. George's and the National Heart Hospitals, Lecturer, and formerly Dean of the Institute of Cardiology, University of London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 181 pages, $19.50.

BASIC & CLINICAL IMMUNOLOGY—Edited by H. Hugh Fudenberg, MD, Professor and Chairman, Department of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina, Charleston; Daniel P. Stites, MD, Assistant Professor of Medicine and Laboratory Medicine, Director, Immunology Laboratory, University of California, San Francisco; Joseph L. Caldwell, MD, Assistant Research Immunologist, University of California, San Francisco and Fort Miley VA Hospital, San Francisco; and J. Vivian Wells, MD, Senior Staff Specialist in Clinical Immunology, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 653 pages, $12.50.

CLINICAL EXAMINATION—A Textbook for Students and Doctors by Teachers of the Edinburgh Medical School—Fourth Edition—Editor, John Macleod, MB, CH B, FRCP Edin, Head of University Department of Medicine, Western General Hospital, Edinburgh. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 491 pages, $15.00.

CORRELATIVE NEUROANATOMY & FUNCTIONAL NEUROLOGY—16th Edition—Joseph G. Chusid, MD, Associate Clinical Professor of Neurology, College of Physicians and Surgeons, Columbia University; Director of Department of Neurology, St. Vincent's Hospital and Medical Center; Associate Attending Neurologist, Columbia-Presbyterian Medical Center, New York City. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 434 pages, $10.00.

CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Fourth Edition—C. Henry Kempe, MD, Professor of Pediatrics and Microbiology, University of Colorado School of Medicine; Henry K. Silver, MD, Professor of Pediatrics, University of Colorado School of Medicine; Donough O'Brien, MD, Professor of Pediatrics, University of Colorado School of Medicine; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 1,053 pages, $15.00.

DIABETIC COOKING MADE EASY—Virginia M. Donahoe. Burgess Publishing Company, 7108 Ohms Lane, Minneapolis (55435), 1973. 72 pages, $3.95.

THE DOCTOR-PATIENT RELATIONSHIP—Second Edition—Kevin Browne, MB, BS, DObst, RCOG, DCH, MRCGP, General Practitioner, Hillingdon; Paul Freeling, MB, BS, FRCGP, General Practitioner, Southall; Foreword by William A. R. Thomson, MD, Formerly Editor of **The Practitioner.** Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 101 pages, $7.50.

DRUG TREATMENT—Principles and Practice of Clinical Pharmacology and Therapeutics—Edited by Graeme S. Avery, Editor-in-Chief; Australasian Drug Information Services Pty Ltd, Sydney & Auckland; Editor: **Drugs, Clinical Pharmacokinetics.** Publishing Sciences Group Inc., 162 Great Rd., Acton, MA (01720), 1976. 1,048 pages, $25.00.

ELEMENTS OF MEDICAL GENETICS—Fourth Edition—Alan E. H. Emery, MD, PhD, DSc, FRCP(E), MFCM, FRS(E), Professor of Human Genetics, University of Edinburgh. University of California Press, 2223 Fulton Street, Berkeley, CA (94720), 1976. 251 pages, $4.25 (paperback).

EPIDEMIOLOGY IN MEDICAL PRACTICE—D. J. P. Barker, MD, PhD, MRCP, MFCM, Senior Lecturer in Clinical Epidemiology, University of Southampton, Honorary Consultant Physician, Royal South Hants Hospital; and G. Rose, DM, FRCP, FFCM, Professor of Epidemiology and Preventive Medicine, St. Mary's Hospital Medical School, Honorary Consultant Physician, St. Mary's Hospital, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 140 pages, $8.00 (Softbound).

EVALUATIONS OF DRUG INTERACTIONS—Second Edition—Prepared by the American Pharmaceutical Association with the cooperation and assistance of the American Dental Association, the American Podiatry Association, the American Society of Hospital Pharmacists, the Food and Drug Administration and the National Library of Medicine. American Pharmaceutical Association, 2215 Constitution Avenue NW, Washington, DC (20037), 1976. 520 pages, $12.50; APhA Member Rate: $8.75.

GANJA IN JAMAICA—The Effects of Marijuana Use—Vera Rubin, PhD, Director of the Research Institute for the Study of Man, Director of the University Consortium for Caribbean Studies and Clinical Associate Professor of Psychiatry, New York Medical College; and Lambros Comitas, PhD, Professor of Anthropology and Education, Teachers College, Columbia University, Associate Director of the Research Institute for the Study of Man. Anchor Books/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 240 pages, $2.95 (Paperback).

THE HEREDITY FACTOR—Genes, Chromosomes, and You—William L. Nyhan, MD, PhD, with Edward Edelson. Grossett & Dunlap, Inc., Publishers, 51 Madison Ave., New York City (10010), 1976. 320 pages, $12.95.

(Continued on Page 19)

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HERESIES—Thomas Szasz, MD, Professor of Psychiatry, State University of New York Upstate Medical Center, Syracuse. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 183 pages, $2.95 (Paperback).

HUMAN REPRODUCTION—The Core Content of Obstetrics, Gynecology and Perinatal Medicine—Second Edition—Ernest W. Page, MD, Professor and Chairman, Department of Obstetrics and Gynecology, Rutgers Medical School; Claude A. Villee, PhD, Andelot Professor of Biological Chemistry, Harvard Medical School; and Dorothy B. Villee, MD, Assistant Professor of Pediatrics, Harvard Medical School. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1976. 471 pages, $15.50.

HYSTERECTOMY—A Complete, Up-To-Date Guide to Everything About It and Why It May Be Needed—Nancy Nugent. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 181 pages, $6.95.

LIVINGSTONE'S POCKET MEDICAL DICTIONARY—Twelfth Edition—Editor: Nancy Roper, SRN, RSCN, RNT, Formerly Examiner to the General Nursing Council for England and Wales. Churchill Livingstone, Edinburgh, London and New York, 1974. Reprinted by Charles Scribner's Sons, 597 Fifth Avenue, New York City (10017), 1976. 592 pages, $3.95 (Paperback).

A MANUAL OF HUMAN ANATOMY—Volume II: HEAD AND NECK—Third Edition—J. T. Aitken, MD, Professor of Anatomy at University College, London; G. Causey, MB, FRCS, Professor Emeritus, University of London; J. Joseph, MD, DSc, FRCOG, Professor of Anatomy at Guy's Hospital Medical School, London; and J. Z. Young, MA, DSc, LLD, FRS, Professor Emeritus, University of London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 194 pages, $11.00.

THE MITRAL VALVE—A Pluridisciplinary Approach—Editor: Daniel Kalmanson, MD, Director of Clinical Teaching, Chief, Department of Cardiology, Cardiovascular Research Center ARNTIC, Foundation A. de Rothschild, Paris. Publishing Sciences Group Inc., 162 Great Rd., Acton, MA (01720), 1976. 576 pages, $25.00.

MODERN STOMA CARE—Edited by Frank C. Walker, MD, ChM, FRCS, FRCS(Edin), Consultant Surgeon, Cleveland Area Health Authority; Hunterian Professor of the Royal College of Surgeons of England; Fellow of the Association of Surgeons of Great Britain and Northern Ireland. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 193 pages, $22.50.

MORAL PROBLEMS IN MEDICINE—First Edition—Edited by Samuel Gorovitz, Senior Editor, Department of Philosophy, University of Maryland, College Park; Andrew L. Jameton, Department of Philosophy, State University of New York at Binghamton; Ruth Macklin, Department of Philosophy, Case Western Reserve University; John M. O'Conner, Department of Philosophy, Case Western Reserve University; Eugene V. Perrin, MD, Department of Pathology, Children's Hospital of Michigan; Beverly Page St. Clair, School of Medicine, Case Western Reserve University; Susan Sherwin, Department of Philosophy, Dalhousie University. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1976. 552 pages, $11.50.

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Panelists

PHILLIP M. BENARON, MD, Chief of Pediatric Cardiology at Santa Clara Valley Medical Center.

DAVID A. BURTON, MD, Assistant Professor of Orthopedic Surgery, Stanford University Medical Center.

SHARRELL MUNCE, MA, Director, Childrens' Trauma Center, Children's Hospital and Medical Center, Oakland, California.

LEE COLEMAN, MD, A Berkeley psychiatrist who authored a professional statement which was received and considered by the California Supreme Court in the psychotherapists' case.

RICHARD J. KOHLMAN, JD, Appellate counsel for plaintiff in the battered child case and visiting lecturer at the School of Law, University of Santa Clara.

JAMES V. BURCHELL, JD, a San Francisco trial lawyer who represented one of the defendant health care providers in the psychotherapists' case.

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RURAL PRACTICE OPPORTUNITIES THROUGHOUT THE INTERMOUNTAIN WEST. Information on communities, practices and placement assistance offered free of charge by University of Utah College of Medicine. Great area for outdoor activities, family life and medical practice. Contact Dr. R. Woolley, Department of Family and Community Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132. (801) 581-5223.

INTERNAL MEDICINE FACULTY POSITIONS UNIVERSITY OF CALIFORNIA, FRESNO, CA. The University of California, San Francisco School of Medicine, is searching for faculty members to join a new Internal Medicine teaching program for medical students, housestaff and associated health professionals at its affiliated VA Hospital in Fresno, California. The Medical School is developing a major clinical branch in Fresno to serve the Central San Joaquin Valley area of California. The VA Hospital in Fresno will be one of its principal teaching facilities. The program emphasizes primary care training. Candidates should have board certification in Internal Medicine and clinical teaching experience. General internists and subspecialists in cardiology, gastroenterology, endocrinology, and pulmonary diseases are sought. Salaries commensurate with academic qualifications and clinical experience. Academic appointments at UCSF School of Medicine. The University of California is an Equal Opportunity Employer with an affirmative action faculty recruitment program. Please send c.v.'s or inquiries for further information to: Lloyd H. Smith, Jr., MD, c/o David Werdegar, MD, Associate Dean, U.C. Medical Education Program, 2615 E. Clinton Ave., Fresno, CA 93703; (209) 224-3235.

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1-606-255-4431

PHYSICIANS WANTED

INTERNIST AND FAMILY PRACTITIONER needed to replace retiring member of Six man Medical Corporation. Small metropolitan area. Very friendly with close proximity to big Cities and beaches. Local City College and 4 year College with all social amenities and sport. 4½ day week, prepaid malpractice, on call shared by all in group. Competitive salary 1st year—full corporate stock holdership after 1st year. Full Corporate benefits immediately. Write: B. R. Ericsson, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

INTERNIST—Board certified or eligible, any subspecialty interest, to join young group in consultative and primary care practice. Located in the foothills in Northern California, a recreation paradise. Contact Oroville Internal Medicine Medical Group, 2767 Olive Highway, Suite 11, Oroville, CA 95965; Phone (916) 533-1554.

INTERNISTS needed in an innovative multi-specialty group practice being organized at the Long Beach VA Hospital for delivery of comprehensive primary patient care. Activities include inpatient care, ambulatory care, and teaching. Contact Chief, Medical Service, VA Hospital (111) Long Beach, CA 90822. An equal opportunity employer.

CHILD PSYCHIATRIST $34,068-$41,352 per year. Stanislaus County Mental Health Department, Modesto, CA. Contact Personnel Department, 1100 H Street, Modesto, CA 95354; (209) 526-6341.

PSYCHIATRIST $32,460-$39,396 per year. Stanislaus County Mental Health Department, Modesto, CA. Contact Personnel Department, 1100 H Street, Modesto, CA 95354; (209) 526-6341.

CALIFORNIA—BOARD CERTIFIED, ANESTHESIOLOGIST for Chief, Anesthesia Section needed at VA Hospital, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position will be available in early December. Salary dependent on experience and qualifications. Contact: Byron V. Whitney, MD, FACS, Chief, Surgical Service, VA Hospital, Livermore, CA 94550; Tel: (415) 447-2560, ext. 213.

CALIFORNIA—ASSISTANT CHIEF OF RADIOLOGY, UCSF-affiliated hospital. Sub-specialty training in Neuro, Peds, or significant experience in lesser sub-specialty areas desirable. Outstanding professional opportunity in an academically oriented clinical practice. Reply to Justin L. Williams, MD, Chief of Radiology, Valley Medical Center of Fresno, 445 S. Cedar Ave., Fresno, CA 93702; (209) 251-4833, 2318.

OBSTETRICIAN to associate with Ob-Gyn Department of established multispecialty group in St. Paul-Minneapolis and suburban areas. Excellent salary, generous fringe benefits. Tremendous growth potential in one of America's leading metropolitan areas. Curriculum vitae and references invited. Box 80100, St. Paul, Minnesota 55108.

INTERNIST—MEDICAL DIRECTOR

Internist sought for full time academic position to serve as Medical Director of home care program and consultant in comprehensive medical clinic within the division of ambulatory and community medicine UCSF. Applicants should have experience in undergraduate teaching and interest in the management of chronic illness in ambulatory and homebound patients. Applicants must be certified in internal medicine and licensed in the State of California.

This position is at the assistant professor level and is available 1 July 1977. UCSF is an Equal Opportunity/Affirmative Action employer. Women and minorities are encouraged to apply. Address inquiries with C.V. to:

John J. Deller, MD, Chairman of Search Committee, Division of Ambulatory and Community Medicine, University of California, San Francisco A-405, before 31 January 1977.

PLASTIC SURGEON

Very nice Southeastern city now in need of a plastic surgeon. The location is Columbus, Georgia. This is an excellent practice opportunity! For further information send C.V. to: **Paul J. Holley, General Care Corp., 6213 Charlotte Ave., Nashville, Tenn. 37209**

PHYSICIANS WANTED

BAY AREA—LOS ANGELES—Specialty open—A major ethical Pharmaceutical Company has 2 newly created positions geographically located in the above areas. Responsibilities include contacts with State Health Agencies, Medical Programs, H.M.O.'s, Legislatures, Medical & Pharmacy Associations, Drug Abuse Programs, Consumer Groups etc. Salary, Bonus & a Car offered. For more information contact A. W. Blendow, 185 Front St., Suite 205, Danville, CA 94526, or call collect (415) 837-8115.

GENERAL INTERNIST, Internist, Certified or or recently trained, for 100 bed Medical Service in Bay Area GM&S Hospital. Excellent research facilities available. Write Chief of Medicine, Veterans Administration Hospital, Livermore, CA 94550.

INTERNIST to join 3 Internists who share office. Present 4th Internist is retiring at end of 1976. Reply: Drs. Martin, Thompson, & Fukuda, 307 Placentia, No. 103, Newport Beach, CA 92663.

PHYSICIANS WANTED

FAMILY/GENERAL PRACTICE—Several positions available in multi-specialty fee for service group; salary and incentive compensation with opportunity for partnership. Clinic is located in Tacoma, WA, near several hospitals. Contact Donald Reddington, Administrator. Mail—Western Clinic, 521 So. "K" St., Tacoma, WA 98405. Telephone (206) 627-9151, ext. 210.

SEEK CERTIFIED INTERNIST FOR SPACE SHARING ARRANGEMENT. Immediate need due to recent disability of active internist. Cardiology, pulmonary, endocrinology or infectious disease background desirable, but practice predominately general internal medicine. Excellent hospital facilities and local amenities. Contact D. Gornel, MD, Box 6447, Carmel, CA 93921 (408) 624-8569.

FAMILY PRACTICE RESIDENCY (FP_1 FP_2) positions available in new program at Santa Ana-Tustin Community Hospital, a new 299 bed facility; program affiliated with University of California, Irvine, School of Medicine, Department of Family Practice; applications from qualified candidates are welcome; minorities and women are encouraged to apply. For application and information write to: Ann K. Kershnar, MD, Director of Medical Education, Santa Ana-Tustin Community Hospital, 1001 North Tustin Avenue, Santa Ana, CA 92705.

SANTA ANA-TUSTIN COMMUNITY HOSPITAL, in cooperation with the College of Medicine of the University of California, Irvine, is recruiting a Director for the Family Practice Residency Program. The program is affiliated with the College of Medicine; Director will hold position there in the Department of Family Medicine, at the Assistant or Associate Professor level. Board certification or qualification required. Duties to include inpatient attending rounds and supervision and teaching in adjacent ambulatory center. Applications from qualified candidates are welcome; minorities and women are encouraged to apply. Send C.V. and names and addresses of three references to Ann K. Kershnar, MD, Director of Medical Education, Santa Ana-Tustin Community Hospital, 1001 N. Tustin Ave., Santa Ana, CA 82705.

URGENTLY NEEDED—FP, Ophth., Urol., ENT, Orth., OB. Beautiful town in N.E. Miss., with large drawing area. On Pickwick Lake and Tombigbee Waterway. Fully equipped hospital. Full-time E. R. coverage. Call collect (601) 423-6014 for Dr. Kelly Segars.

PHYSICIANS WANTED—PART TIME: General practitioner daily 10-1; eye, nose, and throat 4 hours once each week; eye doctor 4 hours once each week. Contact Don Won Kim, KOA Medical Center, 3544 West Olympic Blvd., Los Angeles, CA 90019. (213) 731-0681.

PRIMARY CARE PHYSICIANS NEEDED in Alaska, Idaho, Oregon and Washington. Positions available in Migrant clinics, Community health centers, and other programs in medically underserved areas. Nonprofit organization is coordinating recruitment under federal grant. For information contact: The Clearinghouse, 1370 Stewart St., Seattle, WA 98109, (206) 682-3780.

EVERGREEN STATE NEEDS PRIMARY CARE—Physicians needed in Washington State for group, associate and solo practices. Opportunities exist in rural and urban communities. Nonprofit organization is coordinating recruitment for the state. Contact: The Clearinghouse, 1370 Stewart Street, Rm 210, Seattle, WA 98109. (206) 682-3780.

FACULTY FOR EMERGENCY MEDICINE RESIDENCY PROGRAM, university affiliated teaching hospital. Board Certified in Surgery, Internal Medicine or recent graduate-approved residency in Emergency Medicine. Salary competitive; malpractice insurance paid. California license necessary. Send currculum vitae and names of three references to: William G. Malette, MD, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305. Telephone (805) 323-7651, extension 346.

WANTED—Family practitioner, pediatrician, or Internist to join general surgeon doing family practice in Southwest Minnesota community of 11,000. University town—accredited hospital under new construction. Please contact: R. W. Taintor, MD, 1104 E. College Drive, Marshall, MN 56258. Phone: (507) 532-2251 (Clinic); (507) 532-5281 (Home).

PHYSICIANS

Private practice (solo, partnerships, groups) opportunities exist in many communities of the United States.
As a public service to the communities we serve, we are performing a free, no obligation, service acting as a liaison between physicians interested in practice opportunities and communities in need of their services. All communities have modern, JCAH approved hospitals, modern offices, and recognized needs for additional physicians.
Write with cv, stating availability date, geographical preference, type of practice situation and size of community desired to:

Kenneth W. Oliver
Coordinator, Professional Relations
Hospital Corporation of America
One Park Plaza
Nashville, Tennessee 37203

PHYSICIANS WANTED

CARMEL—Primary care physician needed in this growing resort area. Suite in well located medical-dental complex, to be designed by leasee. Available immediately. (408) 624-1528.

TRYING TO RELOCATE? Texas Positions for Primary Care Physicians require eligibility for Texas licensure and/or completion of FLEX. No charge to the physician. All inquiries confidential. The Rural Doctor's Group, Inc. (A Physician Search/Placement Service), First Federal Place, Suite 507, 200 E. Tenth Street, Austin, Texas 78701.

ASSOCIATE WANTED IN ORTHOPAEDIC PRACTICE. Solo practitioner interested in associate of similar training and interests. Located in small Northern California town, with excellent family and recreational opportunities. Rotating emergency call schedule shared with four other orthopaedists. University trained. Board certified. Special interest in short term Christian Missions. Write Box No. 9499, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

FULL-TIME EMERGENCY ROOM PHYSICIAN for an East Bay (San Francisco Bay Area) hospital to work 40 hour week. Reply to: Emergency Room Director, Box 9497, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PART-TIME EMERGENCY ROOM position available for a well-trained General Practitioner desirous of developing private practice in the East Bay (San Francisco Bay Area). Reply to: Emergency Room Director, Box 9498, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

STOCKTON-SAN JOAQUIN COUNTY. 260-bed teaching hospital in need of Board eligible/certified radiologist. Individual or group association available. Salary open based on experience and qualifications. Malpractice provided by hospital. Located in San Joaquin Valley, east of San Francisco Bay Area. Send C.V. or inquiries to: Michael N. Smith, Director, San Joaquin General Hospital, P.O. Box 1020, Stockton, CA 95201.

YOUNG GENERAL INTERNIST; full-time for teaching in-patient and ambulatory care in Family Practice Residency Program. Northridge Hospital Family Practice Center, 18406 Roscoe Blvd., Northridge, CA 91325. (213) 885-1261.

ANESTHESIOLOGIST

Join two man group in new 300+ bed community hospital—Ozark Area—a paradise of recreational activities, fine pleasant community atmosphere. Desirable environmental situation. Town 65,000—Area 300,000. **Edward J. Safranek, MD, 216A North Greenwood Avenue, Fort Smith, Arkansas 72901.**

PHYSICIANS WANTED

DAVIS-YOLO COUNTY: 4 person family practice group seeking new associate. All MD's Board-certified, in an attractive medical complex, vacation and post-grad leave. Retirement plan. Community hospital accredited in a university town with a medical school. Atmosphere rural suburban. Salary first year, insurance paid. Contact: J. Thomas Wilkes, MD, Davis Medical Group, 635 Anderson Road, Suite 10, Davis, CA 95616 or phone (916) 753-3346.

OPHTHALMOLOGIST—Surgeon to join eye group. Prefer general ophthalmologist with subspecialty (not retina or plastics). Central California University town. Qualified retirement plan, and other corporate benefits. Send résumé to Box 9495, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ER PHYSICIANS, FAMILY PRACTITIONERS, AND PEDIATRICIANS needed for 50 Physician multi-specialty practice. Contact Max F. Kersbergen, Administrator, The Alaska Clinic, 2841 DeBarr Road, Anchorage, Alaska 99504.

WANTED: FAMILY PRACTITIONER AND OB-GYN SPECIALIST in McMinnville, Oregon in the Willamette Valley 35 miles from Portland. In the middle of hunting and fishing area. 13,000 population, 40,000 drawing area. Modern open staff hospital. Dr. James D. Treneman, 1300 N. Adams St., McMinnville Ore. 97128. Phone (503) 472-4647, eves. (503) 472-7676.

POSITION AVAILABLE. OB-GYN for busy clinic. Duties include: family planning; 1st and 2nd trimester abortions; general gyn; laparoscopic tubal ligations; pre-natal and obstetrical care. Salary: $50,000 annually. Medical malpractice paid. Contact: Pat Miller, Family Planning Alternatives, 505 W. Olive Ave., Ste. 210, Sunnyvale, CA 94086.

EXCELLENT OPPORTUNITY for qualified, ambitious Family Practitioner. Full or part-time associate needed for long established private practice in South Bay area of Los Angeles. Participate on percentage basis. Excellent climate, schools, recreation. (213) 373-7369, L. Valkenburg, Bus. Mgr.

INTERNIST AND GENERAL PRACTITIONER: small, well established medical group in San Fernando Valley needs help to service expanding practice. Potential for early partnership. New clinic building with room for expansion. Contact R. C. Hurn, Administrator: 9628 Van Nuys Blvd., Panorama City, CA 91402, telephone (213) 893-9761.

GENERAL PRACTITIONER'S OFFICE IN SALINAS, CALIFORNIA. Fully equipped and furnished. Reasonable. Will turn over records. Phone (415) 344-4442. Or write Box 9501, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

HELP WANTED MEN/WOMEN

MEDICAL CONSULTANT, State Board of Medical Quality Assurance, $36,936-$42,156. Statewide openings with California State Board of Medical Quality Assurance for Medical Consultants to administer program of evaluating and investigating professional conduct and competence of licensees. Must possess license or qualifications for license to practice medicine in California. Five years in general practice medicine and surgery or in one of the specialties, excluding internship, with at least two years experience as member of (1) medical records review board, (2) State board of medical quality assurance, or (3) formal body charged with review of standards or criteria of medical care. Possession of masters degree involving public policy or public health orientation may be substituted for the two years of specialized experience. Applications (résumé) must be received no later than December 24, 1976. Address to Joseph P. Cosentino, MD, Board of Medical Quality Assurance, 1430 Howe Ave., Sacramento, CA 95825. Further information: (916) 322-2341. Equal Opportunity In Action!

(Continued on Page 22)

(Continued from Page 21)

SITUATIONS WANTED

GENERAL SURGEON, 54 years of age, experienced in chest and peripheral vascular surgery, wishes to return to rural living. Pacific Coast States preferred. All replies considered and answered. Write Box 9492, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PULMONARY INTERNIST 33, FMG, ABIM certified completing Fellowship in June 77. Fully trained including Fibreoptic bronchoscopy. Practice type flexible. Available in July 77. Write Box No. 9500, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OPHTHALMOLOGIST: 60-year old, certified, excellent health. Extensive clinical experience with 350 intraocular lens implants. Considering semi-retirement in Southern California. Interested in assisting in microscopic surgery and lens implants. Will not consider full-time practice. Licensed in California. Write Box 9496, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICES FOR SALE

INTERNAL MEDICINE practice for sale. Leaving for academic position in May 1977. Will introduce to patients. Price negotiable. Contact: J. Schneider, MD, 5011 Geary Blvd., San Francisco, CA 94118. Phone (415) 661-5184 after 6 p.m.

EXCELLENT OPPORTUNITY

RETIRING GENERAL PRACTITIONER will lease building and or equipment. No charge for practice. Will turn over records and notify former patients. Come to Redding near Shasta Lake. Hunting, fishing, water and snow skiing. Excellent hospital facilities. Call (916) 243-5455 or write: M. J. Murphy, MD, 3250 Churn Creek Rd., Redding, CA 96001.

SEMINAR IN HAWAII

APRIL 1977 IN HAWAII—ADOLESCENCE SEMINAR. Designed for physicians who care for adolescence. Write W. Schiner, Workshop Coordinator, 1319 Punahou Street, Honolulu, HI 96826.

VACATIONS/MEDICAL PROFESSIONALS TAX DEDUCTIBLE VACATIONS FOR MEDICAL PROFESSIONALS

Over 500 listings of national/international meetings in the medical sciences for 1977. Send a $10 check or money order payable to **Professional Calendars, P.O. Box 40083, Washington, D.C. 20016.**

PHARMACY WANTED

PHARMACIST wishes to establish pharmacy in Clinic, Medical building, Hospital or group of Doctors who want a pharmacy with, or without partnership. Contact Allen H. Fox, 1916 Malcolm Ave., Los Angeles, CA 90025; (213) 279-1231.

FOR RENT—HAWAII

KAUAI, HAWAII, KIAHUNA, Poipu Beach: Condominium apartment. $410 per week for 4 people. Just a step to the ocean. Inquiries Cathy McCafferty—days (415) 393-2000.

RANCH SITES FOR SALE

SONOMA COUNTY RANCH SITES. On south facing hilltops, just 6 miles west—the cooler side—of Healdsburg. Convenient 75 miles north of San Francisco over scenic Redwood Highway 101 Freeway. Nearby shopping Healdsburg and Santa Rosa, yet secure and out of the way. Superb views, scattered meadows, oaks, redwoods and firs. Underground water. Nearby electricity may be brought in. Partially fenced. Pasture for stock and riding on adjoining, larger, retained property by arrangement. Compare with Sierra and desert property values! Three contiguous acreages: 40 acres at $39,000.00, 40 acres at $44,000.00, and 200 acres at $175,000.00. R. Allan Forsyth—Forsyth-Clyde Realty, 6601 Commerce Blvd., Rohnert Park, CA 94928. (707) 544-6359.

SUITES FOR LEASE

CENTRAL ORANGE COUNTY HIGH RISE: Adjacent to large community hospital, ultra modern professional suites available, multi-specialties. Contact John Sainsevain, developer, at (714) 835-6003, 801 N. Tustin Ave., Santa Ana, CA 92705.

OFFICE AVAILABLE

Design Your Ideal Practice

Professional partnership seeks physicians interested in participating in a new condominium office building in Milpitas. Noncompetitive location on best corner site in city. Ten minutes' drive to Alexian Brothers Hospital. Sound investment opportunity for GP, FP, internist or other physician. First owner of suite can accelerate depreciation and obtain other tax benefits. Present physician to patient ratio of 1 to 5,000 in Milpitas, and 6 established dentists will refer new patients.

For details call or write:

FREDERICK SIEMON, DDS
(408) 946-0777
210 S. Main Street, Suite 2
Milpitas, CA 95035

OFFICES FOR LEASE OR RENT

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

CALIFORNIA—Woodland. Custom designed suite for lease in new medical-dental building across street from hospital and major medical clinic. Contact: Woodland Dental Group, 1204 Cottonwood Street, Woodland, California 95695. Phone (916) 662-5485.

MEDICAL SUITE—651 sq. feet, corner in complex with 4 Internists, 2 GP's, Orthopedist, Clinical Laboratory, Dentist, Physical Therapist, Maintenance, all utilities excepting electricity furnished. I. N. Tucker, MD, 25 Evergreen, Mill Valley, CA 94941. Tele: (415) 388-3088.

DESIRABLE LOCATION FOR OPHTHALMOLOGISTS. 4955 Van Nuys Blvd., Sherman Oaks, California. Medical building near freeway, next door to Hospital. Building has pharmacy, bank, doctors, optician. Superb suites—has to be seen to be appreciated. Buckeye Realty & Management Corp. Mr. Richards. (213) 652-1411.

Classified Advertisements

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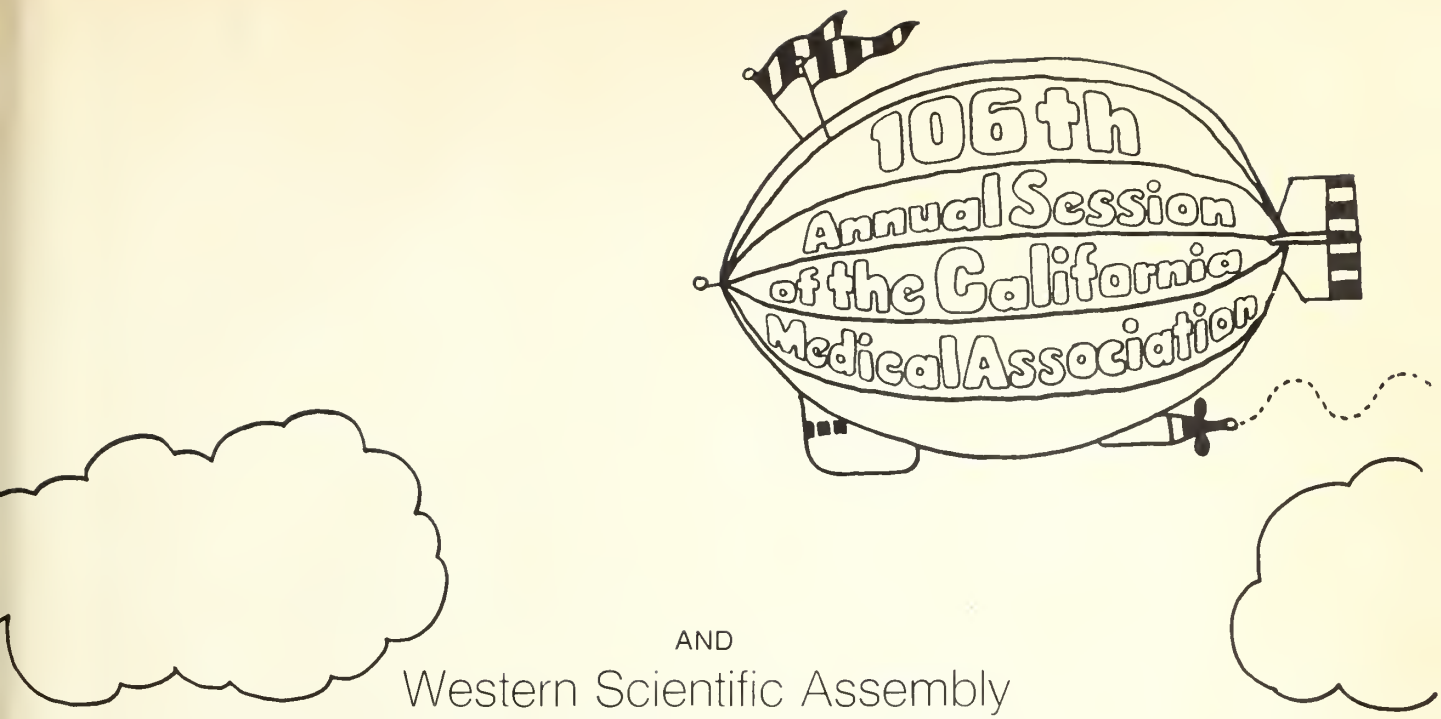

AND

Western Scientific Assembly

March 4-9, 1977 • Disneyland Hotel • Anaheim

Registration opens Friday, March 4 at 7:30 a.m. in the Disneyland Hotel Convention Center Foyer

APPLICATION FOR HOTEL ACCOMMODATIONS

Your reservation request should include the definite date and hour of your arrival and departure.

All suite reservations must be cleared through the CMA Convention Office, San Francisco. If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco 94103.

Cancellations: Please notify Disneyland Hotel Reservations Department of all cancellations.

Changes: All other changes are to be made directly with the hotel at all times.

1977 ANNUAL SESSION • CALIFORNIA MEDICAL ASSOCIATION

Please circle desired accommodations:

DISNEYLAND HOTEL

	Garden	Towers
Single	$30.00	$38.00
Twin or Double	34.00	42.00
Triple or Quad	40.00	48.00
Suites: Sitting Room with 1 Bedroom		90.00
Sitting Room with 2 Bedrooms		125.00

Plus 6% city tax

Parking for registered guests is $1.00 for 24 hours.

If the rate you have requested is no longer available, the next available room category will be confirmed.

Please enclose first night's rent as deposit. Deposit can only be refunded if hotel is notified 5 days before arrival date.

Reservations will not be guaranteed if deposit is not received by February 2, 1977.

Send to: Disneyland Hotel Reservations
1150 West Cerritos Avenue
Anaheim, California 92803

Rate Requested _____

Arrival (date) _____ Hour _____ a.m. p.m. Departure (date) _____ Hour _____ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of **each** person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name _____

Address _____

City and State _____ Zip Code _____

ADDITIONAL OCCUPANTS:

_____

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

CANCER

December 29-30—**Clinical Cancer Symposium.** USC. Wednesday-Thursday.

January 24-28—**Cancer.** STAN. Monday-Friday. $250.

March 6—**Tumors of the Salivary Gland.** Calif. Tumor Tissue Registry at Disneyland Hotel, Anaheim. Sunday. 6 hrs. $100. Contact: Weldon K. Bullock, MD, Ex. Dir., Calif. Tumor Tissue Registry, 1200 N. State St., Los Angeles 90033. (213) 226-4614.

March 16-19—**Modern Concepts in Oncology—5th Annual Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Saturday.

March 19—**Cancer Screening and Cancer Control.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 19—**Tumor Immunology, Clinical Applications.** San Francisco Regional Tumor Foundation at San Francisco. Saturday. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

March 24-25—**Clinical Cancer Conference—11th Annual.** UCSF. Thursday-Friday.

March 25—**Cancer of the Ovary.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

MEDICINE

January 7-9—**Pathogenesis and Treatment of Headache and Other Head Pain in Adults and Children—2nd Annual Course.** American Assn. for the Study of Headache at Hotel del Coronado, Coronado. Friday-Sunday. $225. Contact: Otto Appenzeller, MD, PhD, Dept. of Neurology, UNM School of Medicine, Albuquerque, N.M. 87131. (505) 277-3342.

January 14-15—**Identification of the Fifty Common Dermatoses.** UCSF. Friday-Saturday.

January 15—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

January 17-20—**Ischemic Heart Disease Problems and Perspectives.** Univ. of Hawaii School of Medicine, American Heart Assn., Hawaii Heart Assn. at Royal Lahaina Hotel, Maui, Hawaii. Monday-Thursday. 13 hrs. $175. Contact: Hawaii Conference Services, P.O. Box 22679, Honolulu 96822.

January 21-23—**Advances and Controversies in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, MD 20014.

January 22-23—**Dermatologic Surgery.** See Surgery, January 22-23.

January 23-29—**Topics in Internal Medicine—2nd Annual.** UCSD at Town and Country Hotel, San Diego. One week.

January 24-26—**Cardiac Auscultation.** American College of Physicians at LLU. Monday-Wednesday. 18 hrs. Contact: Registrar of Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 26-28—**Advances in Neurology.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

February 2-April—**Cardiology for the Practicing Internist.** UCLA. Wednesday evenings.

February 3—March 10—**Pulmonary Disease—7th Annual Postgraduate Course.** LLU. Tuesdays.

February 9—**Psychological Effects of Renal Dialysis.** See Psychiatry, February 9.

February 13-17—**Pulmonary Medicine.** UCSF at Lake Tahoe. Sunday-Thursday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

February 14-19—**Pediatric Nephrology and Urology.** See Pediatrics, February 14-19.

February 16-18—**Recent Advances in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 18-19—**Dermatotoxicology.** UCSF. Friday-Saturday.

March 2-4—**Acute Respiratory Failure in Black and White—Annual Postgraduate Course.** California Thoracic Society at Sir Francis Drake Hotel, San Francisco. Wednesday-Friday. 18 hrs. $150 for members; $175, nonmembers. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 11-13—**American College of Physicians—Southern California Regional Meeting.** Vacation Village Hotel, San Diego. Friday-Sunday. Contact: John C. McCall, Jr., MD, 9844-400 Genesee Ave., La Jolla 92037.

March 12—**Echocardiography.** PMC. Saturday.

March 14-16—**Advances in Cardiology.** Foundation for Cardiovascular Research and Hospital of the Good Samaritan at Riviera Hotel, Palm Springs. Monday-Wednesday. 17½ hrs. $200. Contact: Foundation for Cardiovascular Research, 10 Congress St., Suite 203, Pasadena 91105.

March 15-16—**American College of Physicians—Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Contact: Bernard W. D. Fong, MD, 97 Dowsett Ave., Honolulu 96817.

March 17-19—**Cardiovascular Disease—1977: Practical Diagnosis and Management.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

March 21-25—**Arrhythmia Retreat.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

March 21-April 1—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 26—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday.

March 28-April 1—**Consultant's Course in Dermatology.** UCSF. Monday-Friday.

OBSTETRICS AND GYNECOLOGY

January 6-June 30—**Ob-Gyn Review.** UCLA. Thursdays.

January 13-14—**Current Concepts in Prenatal Diagnosis.** UCSD at Hilton Hotel, San Diego. Thursday-Friday.

January 14—**Infections and Septic Shock in Obstetrics and Gynecology.** California Hospital Medical Center, Los Angeles. Friday. 5½ hrs. $15. Contact: Keith P. Russell, MD, Dir., Ob-Gyn Resident Training Program, CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

January 29-February 5—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

February 5-6—**Ob-Gyn Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Miss Dee Davis, Exec. Sec., Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 5-7—**Comprehensive Laparoscopy.** UCSD. Saturday-Sunday.

February 7-11—**Obstetrical and Gynecological Assembly of Southern California.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Monday-Friday. Contact: Miss Dee Davis, Exec. Sec., Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 17-19—**Neonatology.** USC. Thursday-Saturday.

March 18—**Birth Defects, Genetics and the High Risk Patient.** UCD at Sacramento Inn, Sacramento. Friday.

March 18—**Diabetes in Pregnancy.** USC. Friday.

March 25-27—**Gynecological Urology.** USC at Marriott Hotel, Newport Beach. Friday-Sunday.

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MY SPECIALTY (IF ANY) IS ☐ Anesthesiology ☐ Family Practice ☐ Psychiatry ☐ Internal Medicine ☐ OB GYN ☐ Neurology ☐ Radiology ☐ Pathology ☐ Pediatrics ☐ Surgery

STATUS (CHECK ONE): ☐ Private Practice ☐ Hospital Staff ☐ Intern ☐ Resident

PEDIATRICS

January 7-9—**Pathogenesis and Treatment of Headache and Other Head Pain in Adults and Children.** See Medicine, January 7-9.

January 13-16—**Ski and Study Symposium—2nd Annual.** American Academy of Pediatrics, California Chapter 2, at Mammoth Mountain. Thursday-Sunday. 14½ hrs. $125. Contact: AAP, Calif. Chapter 2, P.O. Box 2134, Inglewood 90305.

January 22-23—**Pediatric Urologic Seminar.** Children's Hospital of Los Angeles. Saturday-Sunday. Contact: H. H. Edelbrock, MD, Program Dir., CHLA, P.O. Box 85544, Los Angeles 90027.

January 26—**Adolescent Medicine.** DREW at Martin Luther King Jr. Hospital, Los Angeles. Wednesday.

January 28-30—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 28-30.

February 3-5—**Adolescent Medicine.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday. 21 hrs.

February 14-19—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Saturday.

February 24-26—**Clinical Problems in Pediatrics—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, CHMC, 51st and Grove Sts., Oakland 94609.

March 11-13—**Clinical Pediatrics.** American Academy of Pediatrics, Dist. IX, Chap. II; Childrens Hosp., of L.A.; L.A. Pediatric Society; Childrens Hosp. of Orange County; Southwestern Pediatric Society at Riviera Hotel, Palm Springs. Friday-Sunday. 12 hrs. $100. Contact: AAP, Dist. IX, Chap. II, P.O. Box 2134, Inglewood 90305.

March 25-26—**Pediatric Topics 1977.** UCD at Sacramento Inn, Sacramento. Friday-Saturday.

March 27-31—**Radiological Approach to Pediatric Problems.** See Radiology, March 27-31.

PSYCHIATRY

January 4-March 15—**Intensive Review of Psychiatry and Neurology.** USC. Tuesdays. 40 hrs.

January 4-April 5—**American Board of Psychiatry and Neurology Intensive Review Course—3rd Annual.** UCD. Tuesdays, 7-10 p.m.

January 30-February 4—**Mid-Winter Program for Psychiatrists—3rd Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 5-6—**Clinical Hypnosis and Behavior Modification.** UCLA. Saturday-Sunday. 14½ hrs. $175.

February 9—**Psychological Effects of Renal Dialysis.** UCD at Sacramento Inn, Sacramento. Wednesday.

February 11-12—**Adolescence Today: Psychosocial Issues—3rd National Seminar.** Vista Hill Foundation and Sharp Memorial Hospital at Hotel del Coronado, Coronado. Friday-Saturday. 10 hrs. $65. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

RADIOLOGY AND PATHOLOGY

January 28-30—**Midwinter Radiological Conference—29th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Ronald W. Thompson, MD, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029.

January 28-30—**Radioimmunoassay Symposium.** UCSF. Friday-Sunday.

January 31-February 4—**Computerized Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

February 2-4—**Genitourinary Pathology—4th Annual Course.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 20 hrs. $150. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

February 19-20—**Computerized Scanning of Body and Head—10th Annual Leo G. Rigler Radiology Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday.

March 5-6—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 7-11—**Diagnostic Radiology 1977.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 12-13—**A Practical Course in Ultrasound.** UCSF at Fairmount Hotel, San Francisco. Saturday-Sunday.

March 27-31—**Radiological Approach to Pediatric Problems.** USC at Bonaventure Hotel, Los Angeles. Sunday-Thursday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

January 7-9—**Pathogenesis and Treatment of Headache and Other Head Pain in Adults and Children.** See Medicine, January 7-9.

January 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 14-15—**Surgical Symposium.** Santa Clara County Surgical Society and San Jose Surgical Society at LeBaron Hotel, San Jose. Friday-Saturday. 16 hrs. $125. Contact: Lawrence Stern, MD, 2505 Samaritan Dr., Suite 606, San Jose 95128, (408) 358-1801; or Joseph Brozda, MD, 25 N. 14th St., Suite 460, San Jose 95112, (408) 287-7434.

January 17-21—**Otologic Surgery Course—12th Annual.** Ear Research Institute, Los Angeles. Saturday-Wednesday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 22-23—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

January 22-23—**Pediatric Urologic Seminar.** See Pediatrics, January 22-23.

January 23-27—**Midwinter Clinical Convention.** Research Study Club of Los Angeles at Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: Research Study Club of Los Angeles, Inc., Box 49412, Los Angeles 90049. (213) 879-0143.

January 26-28—**Advances in Neurology.** See Medicine, January 26-28.

January 28-30—**Pediatric Anesthesiology—15th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $125. Contact: Wayne Herbert, MD, Prog. Dir., CHLA, 4650 Sunset Blvd., Los Angeles 90054. (213) 660-2450, ext. 2262.

January 30-February 2—**Theodor Billroth Surgical Anatomy Course.** LLU. Sunday-Wednesday.

January 31-February 4—**Winter Symposium on Emergency Orthopedics.** American College of Emergency Physicians, Calif. Chapter, at Sahara Tahoe Hotel, Lake Tahoe. Monday-Friday. Contact: Stephanie McWilliams, Symposium Coordinator, ACEP, Calif. Chap., 58 California Ave., Orinda 94563. (415) 254-1332.

February 3-4—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 11—**Skin Antisepsis: Chlorhexidine Gluconate.** UCSF. Friday.

February 11-12—**Urodynamic Workshop I: Incontinence and Impotence.** UCLA. Friday-Saturday.

February 12-18—**Mid-Winter Nasal Symposium.** STAN at Harrah's, South Lake Tahoe. One week. $275; $175, residents. Contact: Willard E. Fee, Jr., MD, Division of Otolaryngology, Room 135, Stanford Univ. Medical Ctr., Stanford 94305. (415) 497-5828.

February 22-March 1—**Ventilatory and Circulatory Care of the Seriously Ill Patient.** Calif. Society of Anesthesiologists at Oahu and Kauai, Hawaii. One week. $125. Contact: Norm Catron, CSA, 100 S. Ellsworth St., San Mateo 94401. (415) 348-1407.

February 23-25—**Anterior Segment Disease in Surgery.** USC. 21 hrs. Wednesday-Friday.

February 23-27—**Controversial Areas in Surgery of the Head and Neck.** UCSD at Vacation Village Hotel, San Diego. Wednesday-Sunday. Contact: Alan M. Nahum, MD, 225 W. Dickinson St., San Diego 92103. (714) 294-5910.

March 2-4—**Acute Respiratory Failure in Black and White.** See Medicine, March 2-4.

March 3-4—**Oculoplastic Surgery.** UCSF. Thursday-Friday.

March 3-7—**Controversial Areas in Surgery—14th Annual Seminar.** UCLA at Palm Springs. Thursday-Monday.

March 7-11—**Surgical Forum.** Society of Graduate Surgeons of the Los Angeles County Hospital at Ambassador Hotel, Los Angeles. Monday-Friday. Contact: Miss Dee Davis, Exec. Sec. L.A. Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 8-12—**Vascular Surgery—5th Annual Symposium.** UCLA at Palm Springs. Tuesday-Saturday.

March 10-11—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 11-12—**Ophthalmology Update I.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

March 11-12—**Retinal Disease.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 12 hrs. $125. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 13-17—**American Urological Association, Western Section.** Fairmont Hotel, San Francisco. Sunday-Thursday. 25 hrs. $170 for members; $195, nonmembers. Contact: Frank J. DeSantis, Exec. Sec., 21510 S. Main St., Carson 92037. (213) 549-3470.

March 14-18—**Anesthesiology 1977.** Anesthesiology Educational Foundation at Mammoth Lakes. Monday-Friday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 17-19—**Plastic Ophthalmic Surgery: Intraocular Lenses Insertion.** St. Mary's Hospital and Medical Center, San Francisco. Thursday-Saturday. 24 hrs. $250. Contact: J. A. Sarrail, MD, 450 Sutter St, San Francisco. (415) 397-1500.

March 25-27—**Gynecological Urology.** See Obstetrics and Gynecology, March 25-27.

March 31-April 1—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $150.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

January 8—**Learning to Control Pain.** UCLA. Saturday.

January 8-9—**Family Practice Symposium.** Southern Calif. Permanente Medical Group at Riviera Hotel, Palm Springs. Saturday-Sunday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, Education and Research Dept., 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

January 10-14—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Sheraton-Harbor Island, San Diego. Monday-Friday.

January 10-June 27—**Medical Progress/Medical Practice.** UCSF. Mondays. 7:30-9:30 p.m.

MEDICAL PROGRESS AND MEDICAL PRACTICE

Monday Evenings

January 10-June 27, 1977

Combined Faculty Club-
Millberry Union
University of California
San Francisco

This program is designed to provide an update of the latest developments in Internal Medicine, which have direct relevance to medical practice for the General Internist and the Family Practitioner.

This course is acceptable for 38 hours of Category I Credit towards the certificate in Continuing Education for the California Medical Association and the American Medical Association for registrants who attend the complete course.

Registration Fee is $250.00 (includes special banquet with speaker on March 28, 1977 and a loose leaf syllabus of all lectures). REGISTRATION IN ADVANCE IS ADVISED. $10.00 FEE for refunds requested before course; NO REFUNDS after course begins.

For further information contact:

Extended Programs in Medical Education
University of California
School of Medicine
Room 569-U
San Francisco, California 94143
(415) 666-4251

January 13-14—**New and Old Antibiotics.** USC. Thursday-Friday.

January 13-14—**Medical Aspects of Aging.** UCLA at Valley Hilton, Sherman Oaks. Thursday-Friday.

January 18-21—**Diagnosis and Management of Seizure Disorders.** UCLA at Palm Springs. Tuesday-Friday.

January 22—**Gerontology.** John Muir Hospital and Walnut Creek Based Educational Committee at John Muir Hospital, Walnut Creek. Saturday. Contact: Marshall Y. Kremers, MD, 2528 Ptarmigan Dr., No. 3, Walnut Creek 94595. (415) 938-0568.

January 22-23—**Biofeedback and Meditation: Stress and Self-Regulatory Therapies.** UCSF and The Institute for the Study of Human Knowledge. Saturday-Sunday. 12 hrs. Contact: Ms. Mae Ling Yee, Cont. Ed. in Health Sciences, Room 135G, UCSF. (415) 666-2894.

January 22-February 27—**Basic Acupuncture.** PMC. Saturdays and Sundays. $1,100.

January 24-28—**Emergency Medicine.** UCLA at Beverly-Hilton Hotel, Beverly Hills, Monday-Friday.

January 24-28—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

January 25-28—**New Concepts of Old Diseases.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 29—**Hypertension.** USC. Saturday.

January 31-February 4—**Winter Symposium on Emergency Orthopedics.** See Surgery, January 31-February 4.

January 31-February 5—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 1-5—**Physician and Hospital.** USC at Ahwahnee Hotel, Yosemite. Tuesday-Saturday.

February 5-6—**Clinical Hypnosis and Behavior Modification.** See Psychiatry, February 5-6.

February 6-11—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Sunday-Friday.

February 9-11—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Continuing Medical Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600.

February 9-11—**Conference on Winter Sports Medicine—2nd Annual.** CMA, Medical Foundation of Santa Barbara County and UCLA at Mammoth Mountain. Wednesday-Friday. Contact: CMA.

February 9-12—**Primary Care—Current Management of Common Office Problems.** UCSF. Wednesday-Saturday.

February 11—**Skin Antisepsis: Chlorhexidine Gluconate.** See Surgery, February 11.

February 11-13—**American Medical Association—Regional Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Friday-Sunday. Contact: Mr. G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

February 14-18—**Interpretive Enzymology.** UCSD at Airport Sheraton, San Diego. Tuesday-Saturday.

February 16—**Diagnostic Horizons 1977—15th Annual Symposium.** Eden Hospital at Willow Park Restaurant, Castro Valley. Wednesday. $35. Contact: E. Gregory Thomas, MD, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234, ext. 213.

February 20-25—**Advances in Patient Care—4th Annual Conference.** Medical Communications and Services Assn. at Maui Surf Hotel, Maui, Hawaii. Sunday-Friday. 24 hrs. $175. Contact: Spring Zoog, Conf. Coordinator, MCSA, 315 U-District Bldg., 1107 N.E. 45th St., Seattle 98105. (206) 633-0505.

February 22-26—**Sports Medicine—Ski Injuries.** UCSF at Lake Tahoe. Tuesday-Saturday.

February 26—**Workshop for Physicians and Health Professionals.** UCLA. Saturday.

February 28-March 4—**Basic Science for Clinicians.** STAN. Monday-Friday. $250.

March 4—**Diabetes Program—4th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 4-9—**California Medical Association—106th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Gail Jara, CMA.

March 8-12—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine and American Academy of Family Physicians at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday. 18 hrs. $200. Contact: Mr. Harold Brown, Hawaii Conferences Services, P.O. Box 22670, Honolulu 96822.

March 13-17—**Association for the Advancement of Medical Instrumentation—12th Annual Meeting.** Hyatt Regency Hotel, San Francisco. Sunday-Thursday. Contact: Michael J. Miller, Exec. Dir., AAMI, 1901 N. Ft. Myer Dr., Suite 602, Arlington, Va. 22209. (703) 525-4890.

March 16-April 16—**Family Medicine Tutorial.** DREW. Wednesday mornings.

March 18-24—**LLU School of Medicine—Annual Postgraduate Convention.** Friday-Thursday. Contact: Alumni Association, LLU.

March 26—**Prevention of Athletic Injuries.** Sonoma County Medical Assn. at Calif. State College, Sonoma, Rohnert Park. Saturday. Contact: William E. Tewksbury, Asst. Exec. Dir., SCMA, 3452 Mendocino Ave., Santa Rosa 95401. (707) 544-2010.

March 28-29—**Current Problems in Intensive Care.** UCSF. Monday-Tuesday.

March 28-April 1—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 28-April 1—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation —32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon

Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

Providence Hospital, 700 N.E. 47th Avenue, Portland 97213:

December 22—Staphylococcal Disease: Selected Aspects of Diagnosis and Treatment—8:00 a.m.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Dpartment of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland 97201.

February 14-18—**Family Practice Review.** Sheraton Hotel, Lloyd Center, Portland. Contact: William A. Fisher, MD, Department of Family Practice, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

January 13-14—**Oregon Society for Respiratory Therapy.** Jantzen Beach Thunderbird, Portland. Contact: Jim Lathrope, 2702 N.E. Clackamas Street, Portland 97232.

February 17-19—**Oregon Thoracic Society Annual Chest Disease Conference.** Salishan Lodge, Gleneden Beach, Oregon. Contact: Max R. Mehlhaff, Executive Secretary, Oregon Thoracic Society, 1020 S.W. Taylor St., Portland 97205.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

December 27—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

December 28—**Internal Medicine Review: Adrenal, Pituitary, Gonads.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

January 7—**Medicine and the Law I.** Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

January 11-14—**Fluid and Electrolyte Balance.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. 8 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98410. (206) 756-3152.

January 12—**Pediatrics.** Wednesday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

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For further information, contact:

USC School of Medicine
Postgraduate Division
2025 Zonal Avenue
Los Angeles, CA 90033
Phone (213) 226-2051

January 14—**Newer Approaches to the Same Old Headaches.** Friday. Virginia Mason Medical Center Auditorium. 6½ hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 19—**Perinatal Health Care.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 293-3101.

January 24—**Internal Medicine Review: Hematology.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

January 25—**Internal Medical Review: Hematology.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

January 27—**Internal Medicine Review: Immunologic Renal Disease.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext 258.

January 27—**Radiation-Oncology.** Thursday. 7:30-10:30 p.m., Tacoma General Hospital, Tacoma, Wash. 3 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

January 28—**Internal Medicine Review: Immunologic Renal Disease.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

January 28—**What's New in Liver-Biliary Disease.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 6½ hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 28-29—**Tax, Estate, and Financial Planning.** Friday-Saturday. Olympic Hotel, Seattle. Hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 1—**Surgery: Chest Trauma and Diseases of the Lower Esophagus.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Leonard W. Brewer, MD, 2833 Ft. Missoula Rd., Missoula, MT 59801. (406) 728-6815.

February 2—**Surgery: Chest Trauma and Diseases of the Lower Esophagus.** Wednesday. Univ. of Wash. in Billings, Mont. 1-3.30 p.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (460) 252-2121, Ext 258.

February 4-5—**Modern Concepts of Epilepsy.** Friday-Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 9-10—**University of Washington School of Medicine Circuit Course on Pain.** Feb. 9, Longview, Wash.; Feb. 10, Olympia, Wash. 4 hrs. Physicians, $25; others, $15. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 10-11—**Medical and Surgical Aspects of Urinary Tract Disease.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 13 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

February 11-12—**Coronary Care Ski Weekend.** Friday-Saturday. Big Sky, Mont. Hrs. and fee to be determined. Contact: John Breedon, Exec. Dir., Montana Medical Education Research Foundation, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1491.

February 12-19—**Critical Care: Maternal/Perinatal.** Saturday-Saturday. Univ. of Wash. in Sun Valley, Idaho. 38 hrs. Physicians, $150; others $100. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 15-18—**Gastrointestinal Disease.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. 8 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

February 24-25—**Modern Concepts in Allergy.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours to be determined. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

February 24-25—**Atherosclerosis.** Thursday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

February 24—**Internal Medicine Review: Liver and Pancreatic Diseases.** Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall, 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed. Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

February 25—**Internal Medicine Review: Liver and Pancreatic Diseases.** Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

February 28-March 1—**Emergency Medicine.** Monday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

February 28—**Internal Medicine Review: Ophthalmology for Internists.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 1—**Internal Medicine Review: Ophthalmology for Internists.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, WA 98902. (502) 248-6791.

March 4-5—**Hematology Seminar.** Friday-Saturday. Big Sky, Mont. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

March 9-10—**University of Washington School of Medicine Circuit Course on Pain.** March 9, Bremerton, Wash.; March 10, Everett, Wash. 4 hrs. Physicians, $25; others, $15. Contact: Pat Lind, Div. of CME, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 11—**Cardiovascular Orientation.** Friday. Tacoma General Hospital, Tacoma, Wash. 3 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 12—**Depression and Insomnia.** Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. School of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 16—**Metabolic Disorders in Pediatrics.** Wednesday. Univ. of Wash. in Ancortes, Wash. 7:30-10 a.m., Island Hospital, 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Ancortes, WA 98221. (206) 292-3101.

March 17-18—**What's New in Internal Medicine.** Thursday-Friday. St. Joseph Hospital, Tacoma, Wash. 12 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 18-19—**Otolaryngologic and Head and Neck Emergencies.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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CMA Disability Insurance

Members previously covered by Lumbermens Mutual were transferred on December 1 to a new CMA plan underwritten by Mutual of New York and administered by Marsh & McLennan. Participants have been advised of the change by letter from the Committee on Physicians Group Insurance. If you have overlooked that material, or have any question, please do not hesitate to contact this office.

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Pain: a call to action.

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(II)

*See dosage and administration section of Brief Summary

Whenever an APC/narcotic is indicated.

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (Warning. May be habit forming), 0.38 mg. oxycodone terephthalate (Warning. May be habit forming), 224 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine

INDICATIONS For the relief of moderate to moderately severe pain

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards

Usage in children PERCODAN® should not be administered to children. PERCODAN®-Demi, containing half the amount of oxycodone, can be considered. (See product prescribing information for PERCODAN®-Demi.)

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down

Other adverse reactions include euphoria, dysphoria, constipation and pruritus

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may be occasionally necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCODAN® is given orally. The usual adult dose is one tablet every 6 hours as needed for pain

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants See WARNINGS

Aspirin may enhance the effect of anticoagulants and inhibit the uricosuric effect of uricosuric agents

MANAGEMENT OF OVERDOSAGE Signs and Symptoms Serious overdose with PERCODAN® is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The ingestion of very large amounts of PERCODAN® may, in addition, result in acute salicylate intoxication

Treatment Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonists naloxone, nalorphine or levallorphan are specific antidotes against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

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